6th Annual Meeting of the International Society for Neurovascular Disease

April 29th – April 30th, 2016
New York City, USA

New York Academy of Science
7 World Trade Center
250 Greenwich Street, NY, NY 10007

Program Guide/Agenda

Chairperson of the Annual Meeting: J. Steven Alexander, Ph.D.
Vice-Chair: Felicity Gavins, Ph.D.
Keynote Speaker: Jonathan Kipnis, Ph.D.

ISNVD
International Society for Neurovascular Disease

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Paolo Zamboni, MD Director Vascular Diseases Center Institute of Translational Medicine and Surgery University of Ferrara Ferrara, Italy	**Marcello Mancini, M.D.** Institute of Biostructure and Bioimage National Council of Research Department of Radiology Naples, Italy
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Hector Ferral, M.D. Northshore University Health System Dept. of Radiology, Chicago, USA	**Ms. Carol Schumacher** Director, Annette Funicello Research Fund for Neurological Diseases Menlo Park, California, United States
Ikuo Tsunoda, Ph.D. Chair, Dept. of Microbiology Kindai University, Osaka, Japan	

2 Invited Speakers

Alireza Minagar, M.D. Professor of Neurology Louisiana State University Shreveport, Louisiana, USA	**Chih-Ping Chung, M.D., Ph.D.** National Yang Ming University Taipei Veterans General Hospital Taiwan
Hongyu An, D.Sc Associate Professor, Mallinckrodt Institute of Radiology Associate Director, Center for Clinical Imaging Research Washington University in St. Louis USA	**Hector Ferral, M.D.** Northshore University Health System Dept. of Radiology, Chicago, USA
Dr. Ronald M. Lazar Professor of Neuropsychology (in Neurology and Neurological Surgery) at the Columbia University Medical Center Director, Levine Cerebral Localization Laboratory Columbia University College of Physicians & Surgeons; New York, NY, USA	**Hai Sun, MD, Ph.D.** Louisiana State University Department of Neurosurgery Shreverport, LA, USA
Mat Daemen, Ph.D. University of Amsterdam Amsterdam, the Netherlands	**Mark A. van Buchem, MD** Professor and Chairman Department of Radiology Leiden University Medical Center The Netherlands
Robert Zivadinov, M.D., Ph.D. Professor of Neurology State University of New York at Buffalo Department of Neurology Buffalo, NY, USA	**Felicity Gavins, Ph.D.** Louisiana State University Health Sciences Center Shreverport, Louisiana, USA
E. Mark Haacke, Ph.D. Wayne State University Department of Biomedical Engineering Detroit, MI, USA	**Jonathan Steven Alexander, Ph.D.** Department of Molecular and Cellular Physiology Louisiana State University; Shreveport, LA, USA
Erica Menegatti, Ph.D. Vascular Disease Center University of Ferrara Ferrara, Italy	**Yulin Ge, M.D.** Professor of Radiology New York University School of Medicine New York, NY, USA
Jonathan Kipnis, Ph.D. **KEYNOTE SPEAKER** Center for Brain Immunology and Glia (BIG) University of Virginia Charlottesville, Virginia, USA	**Pierfrancesco Veroux, MD** University of Catania Italy
Marcello Mancini, M.D. Conference Chair Institute of Biostructure and Bioimage National Council of Research Department of Radiology Naples, Italy	**Joel S. Pachter, Ph.D.** Professor of Cell Biology Director, Blood-Brain Barrier Laboratory & Laser Capture Microdissection Core University of Connecticut Health Center Farmington, CT, USA

Francesco Sisini, Ph.D Università di Ferrara Dipartimento di Fisica e Scienze della Terra Ferrara, Italy	**Ivo Petrov, MD, PhD, FESC, FACC** Head of Cardiology, Angiology and Electrophysiology Department City Clinic Heart and Vascular Institute Sofia, Bulgaria
Erica Menegatti, Ph.D. Università di Ferrara Dipartimento di Fisica e Scienze della Terra Ferrara, Italy	**Salvatore Sclafani, M.D.** State University of New York, Downstate Medical Center Brooklyn, NY USA
Paolo Zamboni, MD Director Vascular Diseases Center Institute of Translational Medicine and Surgery University of Ferrara Ferrara, Italy	**Clive Beggs, Ph.D.** Professor of Applied Physiology Leeds Beckett University United Kingdom
Noam Alperin, Ph.D. Department of Radiology University of Miami Miami, Florida, United States	**Harold Rekate, MD** Hofstra Northshore University School of Medicine Long Island, NY, USA
Norman Relkin, MD Weill Cornell Medical College	**Grant Bateman, MD** Director of Magnetic Resonance Imaging John Hunter Hospital, Newcastle Conjoint Associate Professor, Faculty of Health, University of Newcastle Australia
Dr. Eleuterio Toro, OBE, PhD, Dr Hc Laboratory of Applied Mathematics, DICAM University of Trento, Trento, Italy	**Marie-Luce Bochaton-Piallat, Ph.D.** Research Group Leader University of Geneva - Faculty of Medicine Dept. of Pathology and Immunology Geneva, Switzerland

3 PROGRAM AGENDA

FRIDAY, APRIL 29TH, 2016

9:00 a.m. – 9:30 a.m.	**ISNVD President's Address – Dr. Salvatore Sclafani, M.D.; Professor of Radiology, SUNY Downstate, SUNY Update, Nassau University Medical Center**	Introduction by Dr. Margaret Cuomo
9:30 a.m. – 11:00 a.m.	**Session 1: Snapshots of Neurological Diseases with a Neurovascular Perspective: A Neurologic Point of View"**	**Chaired by: Drs. Alireza Minagar and Felicity Gavins**
9:30 a.m. – 9:50 a.m.	"Multiple Sclerosis as a Vascular Disease."	Alireza Minagar, MD, FAAN
9:50 a.m. – 10:10 a.m.	"The Impacts of Cerebral Microbleeds; One Marker of Age-related Cerebral Small Vessel Disease on Congnition and Age-related Functional Impairment."	Chih-Ping Chung, MD, PhD
10:10 a.m. – 10:30 am	"Cognition and Cerebral Hemodynamics in Human Disease."	Ronald Lazar, Ph.D., FAAN, FAHA
10:30 a.m. – 10:45 am	"Neurovascular Imaging in Epilepsy."	Hai Sun, MD, Ph.D.
10:45 a.m. – 11:00 am	**Platform talk #1;** "Longitudinal Magnetic Resonance Imaging of Cerebral Microbleeds in Multiple Sclerosis Patients."	David Utriainen, B.S.
11:00 a.m. – 11:15 am	**Coffee & Pastry Break**	Main Auditorium
11:15 a.m. – 12:40 pm	**Session 2: "Heart & Brain Axis in Neurodegeneration"**	**Chaired by: Drs. Robert Zivadinov and Mat Daemen**
11:15 a.m. – 11:35 am	"The Heart & Brain in Neurodegeneration – an Arterial Perspective"	Mat Daemen, Ph.D.
11:35 a.m. – 11:55 am	"The Heart-Brain Axis from an Imaging Perspective"	Mark A. van Buchem, MD
11:55 a.m. – 12:15 pm	"The Heart and Brain in Neurodegeneration – a Venous Perspective"	Robert Zivadinov, MD, Ph.D., FAAN, FEAN, FANA
12:15 p.m. – 12:30 p.m	**Platform talk #2,** "Arterial Pulse Pressure Waves Causing Endothelium & Myelin Damage may be a Causal Factor in Multiple Sclerosis"	Bernhard HJ Juurlink, Ph.D. Professor Emeritus
12:30 p.m. – 12:45 pm	**Platform talk #3,** "Cerebral Microbleeds in Multiple Sclerosis; A Case-Controlled Study."	Robert Zivadinov, MD, Ph.D., FAAN, FEAN, FANA
12:45 – 2:00 p.m.	**Lunch – On your Own**	Several different restaurants located very close to the meeting venue.
2:00 p.m. – 2:15 p.m.	**"Passing the Torch" – ISNVD President to New President**	Main Auditorium
2:15 p.m. – 4:35 p.m.	**Session 3: "Imaging the Microvasculature"**	**Chaired by: Drs. Mark Haacke and Felicity Gavins**
2:15 p.m. – 2:35 p.m.	"Imaging Cellular Trafficking in the Neurovasculature"	Felicity Gavins, Ph.D.
2:35 p.m. – 2:55 p.m.	"Imaging the Microvasculature Using MRI"	E. Mark Haacke, Ph.D.
2:55 p.m. – 3:15 p.m.	"Gas-enhanced Brain Vascular Imaging"	Yulin Ge, MD
3:15 p.m. – 3:35 p.m.	"Stroke Penumbra Imaging Using a MR Oxygen Metabolic Index"	Hongyu An, D.Sc
3:35 p.m. – 3:50 p.m.	**Coffee Break**	Main Auditorium
3:50 p.m. – 4:05 p.m.	**Platform talk #4,** Designing Novel Imaging Probes for Targeting Inflammatory Lesions in Brain Disorders"	Tamara Boltersdort
4:05 p.m. – 4:20 p.m.	**Platform talk #5,** "Introducing the Next Generation of Microvascular Imaging with a new USPIO-enhanced	Jean-Christopher Brisset, Ph.D.

	MRAV Approach"	
4:20 p.m. – 4:35 p.m.	**Platform talk #6,** "Assessment of an Automated Vein Segmentation Algorithm for MRI Brain Acquisitions at Different Field Strengths"	Giuseppe Palma, Ph.D. for Serena Monti, M.S.
4:35 p.m. – 6:00 p.m.	**POSTER SESSION IN MAIN FOYER**	**Chaired by: Drs. Hector Ferral and Alireza Minagar**
6:00 p.m. – 7:00 p.m.	**KEYNOTE SPEAKER: Jonathan Kipnis, Ph.D., Director, Center for Brain Immunology and Glia (BIG), UVA; "Brain drain, meningeal lymphatics and neurological disorders."**	**Chaired by: Dr. J. Steven Alexander; Vice-President and Conference Chair of ISNVD**
7:15 p.m. – 9:15 p.m.	Welcome Cocktail Reception	Main Foyer

SATURDAY, APRIL 30TH, 2016

8:00 a.m. – 10:05 a.m.	**Session 4: "Asessment of Brain Hemodynamics in the Clinical Setting"**	**Chaired by: Drs. Paolo Zamboni and Marcello Mancini**
8 a.m. – 8:20 a.m.	"Analyzing Micorvasculature Heterogeneity in the Central Nervous System: Microscopy and Molecular Biology Join Forces"	Joel Pachter, Ph.D.
8:20 a.m. – 8:40 p.m.	"Non-Invasive Methods to Measure Venous Pressure and Flow Rate in Jugular by Ultrasound"	Francesco Sisini, Ph.D.
8:40 a.m. – 9:00 a.m.	"Evaluation of Cerebral Hemodynamics with Microbubble-Enhanced Ultrasound Imaging and Magnetic Resonance Imaging in MS Patients"	Marcello Mancini, M.D.
9:00 a.m. – 9:20 a.m.	"The Relationship Between Jugular Flow, Ventricular Volume and Brain Perfusion at SPECT-CT in CCSVI Patients"	Erica Menegatti, Ph.D.
9:20 a.m. – 9:35 a.m.	**Platform talk#7:** "Abnormal Posture Control of Internal Jugular Vein Flow is Associated with Brain Atrophy Progression in MS Patients over 5 years."	Dejan Jakimovski, MD
9:35 a.m. – 9:50 a.m.	**Platform talk #8:** "Automated Real-Time Quantitative Total Cerebral Blood Flow by Phase Contrast MRI"	Noam Alperin, Ph.D.
9:50 a.m. – 10:05 a.m.	**Platform talk #9: "**A semi-automatic Method for Anatomical Measures of the Internal Jugular Veins"	Laura Pelizzari, MSc
10:05 a.m. – 10:20 am	**Coffee and Pastry Break**	Main Auditorium
10:20 a.m. – 12:30 pm	**Session 5: "CSF Disturbances, Aging and Neurodegeneration"**	**Chaired by: Drs. Clive Beggs and Noam Alperin**
10:20 a.m. – 10:40 am	"Cerebral Venous Drainage and its Impact on Cerebrospinal Fluid Motion; A Retrospective Review of the Work of the ISNVD"	Clive Beggs, Ph.D.
10:40 a.m. – 11:00 am	"Origin and Clinical Relevance of the Cranial Spinal CSF Pulsation"	Noam Alperin, Ph.D.
11:00 a.m. – 11:20 am	"Reversal of Periventricular White Matter Intensities in iNPH"	Norman Relkin, MD
11:20 a.m. – 11:40 am	"Cerebralspinal Fluid and Control of Intracranial Pressure"	Harold Rekate, MD
11:40 a.m. – Noon	"NPH, Pseudotumor Cerebri, Leukoaraiosis and Pulse Wave Encelphalopathy"	Grant Batemen, MD

Noon – 12:15 p.m.	**Platform talk #10**: "Discovering the Complex Genetics of Idiopathic Normal Pressure Hydrocephalus"	Leonard Prouty, Ph.D.
12:15 p.m. – 12:30 p.m	**Platform talk #11:** "No Association of Extra-cranial Venous Abnormalities & Clinical Outcomes in MS Patients over 5 years"	Sirin Gandhi, MD
12:30 p.m. – 1:45 p.m.	**Lunch – On your Own**	Several different restaurants located very close to the meeting venue.
1:45 p.m. – 3:50 p.m.	**Session 6: "Vascular Interventions in Neurovenous Disease"**	**Chaired by: Drs. Michael Dake and Salvatore Sclafani**
1:45 p.m. – 2:05 p.m.	"5 Years Experience of CCSVI Endovascular Treatment of a Cardiologist"	Ivo Petrov, MD, Ph.D.
2:05 p.m. – 2:25 p.m.	"Factors Influencing the Efficacy of Balloon Angioplasty in the Treatment Outflow Anomalies of Internal Jugular Veins"	Pierfrancesco Veroux, MD
2:25 p.m. – 2:45 p.m.	"Clinical Outcomes of a Dutch Treatment Registry"	Hector Ferral, MD
2:45 p.m. – 3:05 p.m.	"Reasons for Failure in Neurovenous Interventions"	Salvatore JA Sclafani, MD
3:05 p.m. – 3:20 p.m.	**Platform talk #12:** "Endovascular Treatment and Stem Cell Therapy of CCSVI"	Ivo Petrov, MD, Ph.D.
3:20 p.m. – 3:35 p.m.	**Platform talk #13:** "CCSVI Prevalence in Meniere's Disease and Preliminary Results of Balloon Venous Angioplasty"	Aldo Bruno, MD
3:35 p.m. – 3:50 p.m.	**Platform talk #14: "**Multiple Sclerosis and Symptom Changes after PTA: a 4 year regular follow up on 366 Patients"	Pietro Maria Bavera, MD
3:50 p.m. – 4:00 p.m.	**Dr. Veroux announcement regarding 2017 ISNVD Congress Venue/Video**	**Main Auditorium**
4:00 p.m. – 4:15 p.m.	**Water Break**	
4:15 p.m. – 5:15 p.m.	**Session 7:Annette Funicello Research Fund for Neurological Diseases Grant Awards (Follow-up from last year)**	**Chaired by: Dr. Michael Dake and Mrs. Carol Schumacher**
4:15 p.m. – 4:30 p.m.	"Randomised, double-blinded, controlled (with sham) study of percutaneous Transluminal Angioplasty for Extracranial Vein Stenoses in Patients with Multiple Sclerosis"	Dr. Helen Kavnoudias
4:30 p.m. – 4:45 p.m.	"A Case-Controlled, 5-year Follow-up Study of Cardiovascular, Environmental and Genetic Risk Factors for Disease Progression in Patients with MS"	Robert Zivadinov, MD, Ph.D., FAAN, FANA, FEAN
4:45 p.m. – 5:00 p.m.	"Combined Study of Neurodegeneration, Cerebrovascular Reactivity and Venous Drainage Impairments in Parkinson's Disease (PD) and Multiple Sclerosis (MS)"	Marcella Lagana, Ph.D.
5:00 p.m. – 5:15 p.m.	"Diagnostic and Prognostic Use of Neurolymphatic Biomarkers in Multiple Sclerosis"	J. Winny Yun, Ph.D. Candidate
5:15 p.m. – 5:30 p.m.	**Coffee Break**	Main Auditorium
5:30 p.m. – 7:05 p.m.	**Session 8: "Vascular Function, Glymphatic System and New Drug Development"**	**Chaired by: Drs. J. Steven Alexander & Ikuo Tsunoda**
5:30 p.m. – 5:50 p.m.	"Alterations in Hemodynamic Flow Patterns and Endothelial Dysfunction in Neurodegenration"	J. Steven Alexander, Ph.D. for Luke White, Ph.D.

5:50 p.m. – 6:10 p.m.	"Progress Towards a Global Circulation Mathematical Model, Incorporating detailed CSF and Lymphatics Dynamics"	Eleuterio Toro, Ph.D.
6:10 p.m. – 6:30 p.m.	"Structural Changes in extra-CNS Blood Vessels in Neurodegeneration"	Marie-Luce Bochaton-Piallat, Ph.D.
6:30 p.m. – 6:45 p.m.	**Platform talk #15:** "First Step Towards a Mathematical Model for the Human Lymphatic System"	Christian Contarino
6:45 p.m. – 7:00 p.m.	**Platform talk #16:** "Upregulation of Lymphatic Markers and Vascular Adhesion Molecules in CNS RNAseq Transcriptome of a Viral Model for MS"	Seiichi Omura, Ph.D.
7:00 p.m. – 7:15 p.m.	**Platform talk #17:** "Traumatic Brain Injury (TBI) Severity Quantification and Outcome Prediction Using MRI"	Miller Fawaz, MS
8:00 p.m.	**Gala Dinner Event & Awards Presentation @ Barbalu's Italian Restaurant**	**225-227 Front Street, 10038**

4 FACULTY/INVITED SPEAKER ABSTRACTS

KEYNOTE SPEAKER ADDRESS - ABSTRACT

Brain drain, meningeal lymphatics and neurlogical disorders

Jonathan Kipnis, Ph.D.,
Center for Brain Immunology and Glia (BIG), Department of Neuroscience, School of Medicine, University of Virginia, Charlottesville, Virginia
Keynote Speaker

Abstract:

The central nervous system (CNS) was considered to be devoid of classical lymphatic drainage. We recently challenged that paradigm by demonstrating the presence of a lymphatic vasculature in the surrounding of the brain called the meninges. We demonstrated that lymphatic vessels, expressing hall the markers for lymphatic endothelial cells (LEC; i.e Lyve-1, Prox1, podoplanin, VEGFR3 and CCL21) are located along the dural sinuses. They present features of initial lymphatic through the absence of surrounding smooth muscle cells and lymphatic valves, along with presenting a punctate expression pattern for adhesion molecules (Claudin-5 and VE-Cadherin). Finally, we demonstrated that these vessels drain fluids, macromolecules and immune cells from the cerebrospinal fluid into the deep cervical lymph nodes.

Our recent efforts are concentrated on understanding the role of meningeal lymphatic vessels in CNS function in health and disease. Our results suggest that the drainage into the deep cervical lymph nodes might play different roles at different stages of several neurological diseases. Understanding the function of the lymphatic drainage in CNS might shed a new light on neurological disorders and offer new therapeutic targets.

Dr. Kipnis has nothing to disclose nor any conflicts of interests to declare.

Multiple sclerosis as a Vascular Disease

A. Minagar[1], I. Tsunoda[1,2] and Alexander, J.S. [1,3],
LSUHSC-Shreveport, LA, Department of Neurology[1], Microbiology and Immunology[2], Molecular & Cellular Physiology[3]

For decades, Multiple Sclerosis (MS) has been regarded and researched primarily as a viral-associated or an immune-mediated disease of human central nervous system. The causes of and cure for MS remain elusive and the available disease modifying or immunosuppressive therapies work via general suppression or very pointed and specific suppression of the immune system and blood brain barrier (BBB). A significant and massive research effort focusing on T and B lymphocytes, neurons, astrocytes and oligodendrocytes have illuminated our way into the complex field of MS pathogenesis, but has not assisted neurologists to find the cause or the triggering event in pathogenesis of MS or a permanent cure. Despite clear support for viral or immune contributions from experimental models of MS less significant progress in understanding of MS. Based on a plethora of evidence from patient-based and experimental observations, we propose a different view of MS pathophysiology with main focus on abnormalities of cerebral endothelial cells as the possible origin of MS. Numerous neuropatholgocial studies support the fact that MS, as a vascular disease, is a venous rather than an arterial disease. All of demyelinating lesions of MS exclusively develop at the peri-venous areas. We also are aware that lymphocyte migration through the disrupted endothelial layer of the BBB occurs more frequently at the venous side of brain circulation rather the arterial side. Interestingly, *Natalizumab* (Tysabri), one of the most potent therapies ever developed for MS, can be regarded as a vascular drug acting on the cerebral endothelial cells to block transendothelial migration of the activated lymphocytes. Similar actions of other MS-active drugs at least partially support endothelial targeting as a basis of therapeutic effectiveness. All these evidence support our proposed hypothesis that MS is inherently a "vascular disease" and fundamental abnormalities of the venous system may contribute to MS.

Dr. Minagar has nothing to disclose nor any conflicts of interests to declare.

The Impacts of Cerebral Microbleeds, One Marker of Age-related Cerebral Small Vessel Disease, on Cognition and Age-related Functional Impairment

Chih-Ping Chung, Department of Neurology,
Taipei Veterans General Hospital, National Yang Ming University, Taiwan

The 1st part Cognition

Objective: There are scanty community-based studies of Asian population investigating the relationship between the cerebral microbleeds (CMBs) and many different cognitive domains. The present study, a Taiwan community-based study, evaluated whether the number and location of CMBs had effects on a variety of cognitive functions.

Methods: Study subjects were from the community-based I-Lan Longitudinal Aging Study. Subjects with dementia and stroke were excluded. The cognitive domains including verbal memory, language, visuospatial executive, and verbal executive functions were evaluated. The number and location of CMBs were revealed by the 3T susceptibility weighted imaging MRI.

Results: 401 subjects [63.87(8.82) years, 193(48.1) men] were included. CMBs were found in 11.7% of population. The results showed that lobar CMBs were significantly associated with poorer visuospatial instead of verbal executive function independent of age, gender, education, hypertension and the other markers of cerebral small vessel diseases. Specifically, the presence of CMBs in the temporal and frontal lobe determined worse neuropsychological tests involving the visuospatial executive functions, the complex figure test [temporal CMBs: regression coefficient (95% confidence interval) = -4.59 (-9.46 – -0.35), p = 0.035; frontal CMBs: -2.13 (-6.91 – 2.65), 0.381] and clock drawing test [temporal CMBs: -1.55 (-3.17 – 0.10), p = 0.063; frontal CMBs: -1.48 (-3.15 – 0.18), 0.082]. The CMB numbers were not associated with any cognitive domains.

Conclusion: The location is more important than amounts regarding the CMB effects on cognitive functions in non-demented non-stroke healthy subjects. Lobar CMBs, particular in the temporal and frontal lobe, are associated with poorer visuospatial executive function.

The 2nd part Physical Frailty

Objective: Physical frailty in the elderly are associated with vascular risks factors and usually leads to adverse outcomes, however its pathophysiology is still unclear. The present study aimed to evaluate whether cerebral microbleeds (CMBs), one presentation of cerebral small vessel diseases (CSVDs), are associated with the physical frailty.

Methods: This is a prospective study evaluating in participants from I-Lan Longitudinal Aging Study, a community-based study. The physical frail status was evaluated by the Cardiovascular Health Study score which includes components of weakness, low physical activity, slowness, exhaustion, and weight loss. The CMBs were assessed by susceptibility-weighted-imaging MRI.

Results: There were 962 subjects [62.5 (8.6) years, 425 (44.2%) men] included, 319 (33.2%) physical pre-frail and 32 (3.3%) physical frail. Pre-frail/frail subjects, compared with the robust subjects, had more overall CMB numbers and more number/incidence of CMB in deep and infratentorial regions.

After multivariate analyses adjusting for age, sex and vascular risk factors, CMB numbers were significantly associated with the physical pre-frail/frail status. Brainstem is the only CMB location significantly associated with the physical pre-frail/frail status (OR, 95% CI: 11.85, 2.26-62.12) after

(Chung, cont'd)

adjusting for age, sex, vascular risk factors and the other presentations of CSVDs. The result also showed that CMBs in brainstem was able to predict the weakness component of physical frailty (5.04, 1.47-17.2).

Interpretation: We are the first to show that the overall number and deep/infratentorial location, especially the brainstem, of CMBs are associated with the physical frailty. Our results suggest CSVD being involved in the pathophysiology of physical frailty.

References

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Dr. Chung has nothing to disclose nor any conflicts of interests to declare.

Cognition and Cerebral Hemodynamics in Human Disease

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Most investigators studying vascular cognitive impairment have focused on the impact of stroke, hemorrhage, silent infarction and small-vessel disease. Hemodynamic abnormalities, specifically cerebral hypoperfusion and hyperperfusion, and impaired vasomotor reactivity, are present in a variety of cerebrovascular conditions. The purpose of this presentation is to present the general thesis that structural pathology may reflect permanent, end-organ injury leading to irreparable cognitive decline but hemodynamic causes of cognitive dysfunction may be reversible. Following a brief overview of cerebral hemodynamic mechanisms[1], discussion will then focus hemispheral and whole-brain models of perfusion deficits in human disease. Stenosis in the internal carotid artery can produce loss of cerebral blood flow to either cerebral hemisphere, either acutely[2,3] or over time[4,5], resulting in ischemia, cognitive impairment and cerebral compensation via plasticity. Data will be presented to demonstrate that not only can the brain tolerate long periods of perfusion loss, but that restitution of cerebral perfusion can result in restoration of cognitive function and normalized representation of brain function.[6,7] For models of global hypoperfusion and hyperperfusion, discussion will then focus on the hemodynamic and cognitive impact of congestive heart failure[8,9], the effects of mechanical circulatory support with ventricular assist devices[10], and the consequences of heart transplantation[11]. It will also be shown that perfusion loss to either hemisphere or global hypoperfusion affects a common core of diffusely represented cognitive functions, including processing speed, attention, working memory and executive function.

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Dr. Ronald Lazar has nothing to disclose nor any conflicts of interests to declare.

Neurovascular imaging in Epilepsy

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Neuroimaging is central to the evaluation of patients with epilepsy, especially in the identification of structural brain lesions that can serve as epileptogenic foci, and that might be surgically resectable if the patient becomes refractory to medical treatment. The phenomenon of epileptogenic foci is closely related to changes of cerebral blood flow pattern of the brain. Many neuroimaging techniques such positron emission tomography (PET), single photon emission computed tomography (SPECT) utilizes these changes to help localizes the source of seizure. , Functional neuroimaging studies such as fMRI are also used to map neurologic functions as part of surgical planning to predict and limit postoperative neurologic deficits, including sensorimotor, language and memory function. In addition, we will also discuss other neuroimaging techniques such as magnetic source imaging (MSI) and Glutamate imaging, which are employed to better define the area of functional defect and epileptogenicity, to identify MRI-occult lesions, and to identify the more active lesion in patients with dual or multiple pathologies.

Dr. Hai Sun has nothing to disclose nor any conflicts of interests to declare.

Lack of intracranial atherosclerosis in various atherosclerotic mouse models

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Aims: Although mice are used extensively to study atherosclerosis of different vascular beds, limited data is published on intracranial atherosclerosis. Here, we examined the presence of intracranial atherosclerosis and neuropathological changes in different atherogenic mouse strains and studied differences in vessel wall characteristics in search for possible explanations for the different atherosclerotic susceptibility between extracranial and intracranial vessels.

Method and results: The presence of atherosclerotic plaques was systematically examined from the distal portion of the common carotids to the circle of Willis in three atherogenic mouse models: ApoE$^{-/-}$, ApoE$^{-/-}$ Fbn1$^{C1039G+/-}$ and ApoB100/LDLr$^{-/-}$. Extra- and intracranial vessel characteristics were studied by immunohistochemistry. All three strains developed atherosclerotic lesions in the common carotids, while no lesions were found intracranially. Atherosclerotic plaques were frequently present in the internal carotids, but usually stopped at the bifurcation with the pterygopalatine artery, which coincided with altered vessel morphology. Intracranially, the amount of elastic layers decreased, the internal elastic lamina became thicker, an endothelial cell activation marker decreased, and tight junction marker claudin-5 increased. Stimulation of brain endothelial cells with oxLDL induced endogenous protective antioxidant capacity through a Nrf2-mediated increase of heme oxygenase-1 expression.

In a second study we compared the volume of the whole brain and six anatomical brain structures in one year old ApoE$^{-/-}$ versus C57Bl/6 mice and in one year old ApoE*3L.CETP mice on high-cholesterol diet (HCD) versus chow diet using MRI and performed histological analysis of the brains. Aged ApoE$^{-/-}$ mice showed an increased cerebellar volume and decreased volume of the (hypo)thalamus compared to C57Bl/6 mice. Tight-junction marker claudin-5 was decreased in the cortex and hippocampus, coinciding with increased blood-brain barrier leakage and decreased white matter myelin basic protein. Microgliosis was absent. Although ApoE*3L.CETP mice on HCD had severe aortic atherosclerotic lesions, brain volumes, tight-junctions, blood-brain barrier leakage and Iba-1 expression were not different from ApoE*3L.CETP mice on chow.

Conclusions: *1)* Intracranial atherosclerosis is absent in all three atherogenic mouse models up to the age of 41 weeks. We suggest that differences in brain vessel structure and increased antioxidant capacity of the brain endothelium contribute to decreased atherosclerosis susceptibility of murine intracranial arteries. 2) The discrepancy in the presence of microvascular changes between the severe atherosclerotic ApoE$^{-/-}$ and ApoE*3L.CETP models could indicate a more important effect of the absence of the ApoE gene on cerebral microvascular changes in ApoE$^{-/-}$ mice compared to the effect of extracranial atherosclerosis.

Dr. Mat Daemen has nothing to disclose nor any conflicts of interests to declare.

The heart-brain axis from an imaging perspective

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There is increasing evidence that brain function is influenced by hemodynamic factors. These factors include heart function, aortic stiffness, patency and stiffness of the carotids and vertebral arteries, patency of the circle of Willis, functional and structural status of small cerebral vessels and the neurovascular unit at a capillary level. How these factors, separate and in concert, influence cognition is incompletely understood. Modern imaging techniques allow for in vivo probing individual hemodynamic mechanisms that together influence brain function. In this presentation, an overview will be provided of these imaging techniques as well as of the results that have been obtained in using these techniques to understand the hemodynamic mechanisms influencing cognition.

No conflict of interest or disclosures per Dr. van Buchem.

Heart & Brain in Neurodegeneration –Venous perspective

Robert Zivadinov, MD & PhD[1,2]

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Background: The susceptibility and progression of neurodegenerative disorders may be related to extracranial venous disease. Internal jugular vein (IJV) narrowing has been implicated in central nervous system pathologies, however normal physiological age- and gender-related IJV variance in healthy individuals (HIs), and their relationship to brain MRI outcomes has not been adequately assessed.
Objectives: We assessed the relationship between IJV cross-sectional area (CSA) and aging, and determined its relationship with brain volumes in healthy individuals without neurologic disease (HIwND).

Methods: This study involved 193 HIs (63 males and 130 females) who received 2-dimensional magnetic resonance venography and brain volume 3D-T1 sequences at 3T. The minimum CSA of the IJVs at cervical levels C2/C3, C4, C5/C6, and C7/T1 was obtained using a semi-automated contouring-thresholding technique. Subjects were grouped by decade. Pearson and partial correlation (controlled for cardiovascular risk factors, including hypertension, heart disease, smoking and body mass index) and analysis of variance analyses were used, with paired t-tests comparing side differences. Normalized whole brain volume (NWBV) was assessed. Partial correlation analyses were used to determine associations between IJV CSA and NWBV.

Results: Mean right IJV CSA ranges were: in males, 41.6 mm2 (C2/C3) to 82.0 mm2 (C7/T1); in females, 38.0 mm2 (C2/C3) to 62.3 mm2 (C7/T1), while the equivalent left side ranges were: in males, 28.0 mm2 (C2/C3) to 52.2 mm2 (C7/T1); in females, 27.2 mm2 (C2/C3) to 47.8 mm2 (C7/T1). The CSA of the right IJVs was significantly larger ($p<0.001$) than the left at all cervical levels. Controlling for cardiovascular risk factors, the correlation between age and IJV CSA was more robust in males than in the females for all cervical levels. There was an inverse relationship between NWBV and total IJV-CSA (C7-T1: males $r= -0.346$, $p=0.029$; females $r= -0.301$, $p=0.002$). After age adjustment, association of NWBV and normalized gray matter volume with IJV-CSA became positive in males (NWBV and right IJV-CSA (C2-C3) changed from $r = -0.163$ to $r = 0.384$, $p=0.002$), but not in the females.

Conclusion: In HIwNDs age, gender, hand side and cervical location all affect IJV CSA. These findings suggest that any definition of IJV stenosis needs to account for these factors. Sex differences exist in the relationship between brain volume and IJV-CSA in HIwND.

Key words: multiple sclerosis, MRV, IJV CSA, brain volume

Study disclosure:
None.

Financial Relationships/Potential Conflicts of Interest:

Robert Zivadinov received personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health and Novartis for speaking and consultant fees. He received financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin-Coherus and IMS Health.

Imaging Cellular Trafficking in the Neurovasculature

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Unregulated inflammation plays a crucial role in the pathophysiological cascade of ischemic stroke and related forms of brain injury. It is known that endothelial cell activation as well as consequent recruitment and activation of leukocytes and platelets, all play important roles in promoting cerebral damage in ischemia/reperfusion (I/R) injury. However, although the underlying mechanisms mediating the post-ischemic cerebral damage remain poorly understood, much interest lies in targeting inflammation. One such potential target is the interaction of annexin A1 (AnxA1) with its receptor, formyl peptide receptor 2 (FPR2/ALX).

We investigated potential roles of this mechanism in a murine model of cerebral I/R injury. Using fluorescent intravital microscopy to image cellular trafficking in the neurovasculature, we found that cerebral I/R injury induced increased neutrophil and platelet activation and neutrophil-platelet aggregate (NPA) formation within cerebral microvessels. These effects were coupled with elevations in brain myeloperoxidase and serum pro-inflammatory cytokines in wild-type (WT) mice.

The AnxA1-mimetic peptide, Ac2-26, mitigated I/R induced leukocyte and platelet adhesion in WT mice. Blocking Fpr2/ALX with the antagonist Boc2 reversed this effect, and treatments were ineffective in Fpr2/3 knockout (Fpr2/3$^{-/-}$) mice, who displayed an exacerbated disease severity, as evidenced by increased infarct area, blood brain barrier dysfunction, increased neurological score and elevated levels of cytokines. Furthermore, ASA treatment significantly reduced cerebral leukocyte recruitment, and increased endogenous levels of ATL, effects again mediated by Fpr2/3.

In conclusion, we have used fluorescent intravital microscopy to help quantify cellular interactions in the brain following I/R. Our novel findings demonstrate the importance of the Fpr2/ALX system as a potential therapeutic target for initiating endogenous pro-resolving, anti-inflammatory pathways following cerebral I/R injury.

Summary:
Post cerebral ischemia reperfusion (I/R), inflammation results in endothelial cell activation as well as consequent recruitment and activation of leukocytes and platelets. Dr. Gavins will discuss these concepts and the technique of fluorescent intravital microscopy to visualize and quantify these cellular interactions. Furthermore, she will present data from her laboratory demonstrating that an absence of the formyl peptide receptor 2 (FPR2/ALX) leads to an aberrant inflammatory response to stroke, and that targeting this system may provide a potential therapeutic option for the treatment of ischemic stroke and related forms of brain injury.

Dr. Gavins has nothing to disclose nor any conflicts of interests to declare.

Imaging the Microvasculature Using MRI

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The vascular system is important both morphologically and functionally for neuroscientific studies and clinical applications. Numerous clinical problems such as stroke, dementia, arteriovenous malformations (AVM), tumor evaluation, and traumatic brain injury (TBI) require detailed vascular information for the best diagnostic interpretation. Due to the vast differences in hemodynamic characteristics, pathological behavior, and the underlying MRI principles of vessel-tissue contrast, arteries and veins are usually imaged with separate protocols. Collecting both SWI and MRA leads to increased scan time and motion-related misregistration. Our non-contrast flow rephase/dephase interleaved gradient recalled echo (GRE) sequence avoids any potential registration problems and enables a precise review and a complete picture of the relationship between the two vasculature networks (1). This is accomplished with a subtraction processing method for selective MRA enhancement utilizing the flow rephased and dephased images. SWI and SWIM can be derived from the full flow compensated first echo of this sequence. The exquisite visualization of small arteries offers safe, noninvasive imaging, which is of particular importance in patients with impaired renal function where a contrast agent cannot be used or in whom intravenous access is challenging. This approach should make it possible to visualize vessels on the order of 250µm to 500µm.

Although this MRAV approach is attractive for standard clinical use, it has little chance to study microvascular details in humans *in vivo* with an in-plane resolution of 50-100µm. In vivo detection of tiny arterioles, where vasculogenic neuropathology often begins, remains challenging and uninvestigated. Two (2) major limitations to high resolution microvascular imaging are blood vessel contrast and signal-to-noise (SNR). We propose to overcome these two obstacles based on a microvascular imaging method which we refer to as MICRO MRAV or "Microvascular In-vivo Contrast Revealed Origins: MR Arteriography and Venography". We will use an ultra-small-superparamagnetic-iron-oxide (USPIO) contrast agent (a blood pool agent)[17] called Ferrumoxytol (an FDA approved drug for treating anemia) for imaging the microvasculature down to the level of 50-100µm through the T2* and quantitative susceptibility mapping (QSM) methods. Ferumoxytol provides strong T1 and T2* shortening with R1 and R2 values of 15 and 89 mM^{-1}/sec (2). It acts as a blood pool agent with a blood half-life of nearly 15 hours. It appears to be safe in patients with chronic kidney disease since it is cleared from the circulation primarily by the reticuloendothelial system not the kidney. With low dose of Ferumoxytol, no adverse reactions have been reported in previous MRI studies. Future applications of this work could include microvascular studies of hypertension, cerebral amyloid angiopathy (CAA), and multiple sclerosis (MS). More specifically, our previous studies have shown microvascular abnormalities in MS including: 1) a close perivenular relationship of lesions with venules; *2)* hemodynamic impairment in normal appearing brain; 3) disrupted blood flow regulation; and 4) *diminished medullary venules* in the periventricular region, all of which strongly suggests venous architectural abnormalities. Still, there is no direct evidence of how venous architecture is involved in MS lesions including density, architectural morphology or micro-occlusion is lacking.

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Dr. Haacke will give a verbal disclosure upon presentation.

Gas-enhanced brain vascular imaging

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Normal brain functions are highly dependent on sufficient and carefully regulated blood supply to meet the high neuronal energy demand. Oxygen (O_2) and carbon dioxide (CO_2) play a critical role in brain functioning and metabolism, therefore, changing blood O_2 or CO_2 concentration by inspiring various gas mixtures will affect normal neuronal and vascular physiology, which can be measured in vivo by advanced MRI.

This talk will focus on (1) how to establish a MR compatible gas-delivery system [1] and the associated protocol that allow the delivery of special gas mixtures (e.g., O_2, CO_2, N_2, and their combinations); (2) how to interpret oxygenation-based MRI signals in functional and susceptibility-weighted imaging; (3) how to measure oxygen metabolism using MRI[2, 3]; and (4) what is cerebral vascular reactivity (CVR) imaging using hypercapnia (by breathing 5% CO_2) MRI and its role in clinical applications.

Multiple sclerosis (MS) is considered an inflammatory autoimmune neurologic disease characterized by demyelination and axonal/neuronal degeneration. Recently, there has been emerging evidence linking vascular abnormalities and disease pathogenesis and progression in MS. This talk will also review the applications of several vascular imaging techniques in MS. It will provide a discussion of novel vascular hypotheses related to some imaging findings of vascular involvement in MS including the lesion-vessel relationship[4], blood perfusion changes, and vascular function (i.e., CVR) impairment[5].

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Dr. Ge has nothing to disclose nor any conflicts of interests to declare.

Stroke penumbra imaging using a MR oxygen metabolic index

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Abnormal oxygen metabolism occurs in neurological diseases such as ischemic stroke, intracranial stenosis, carotid occlusion, moyamoya disease, cerebral trauma, and brain tumors. During acute ischemic stroke, "misery perfusion", marked by an elevation of OEF and decreased blood flow, has been used as an indicator of "at-risk" tissue that is a target of therapeutic treatments (Baron, Bousser, Comar, Soussaline, & Castaigne, 1981). On the other hand, indiscriminate treatment without screening for "at-risk" tissue may lead to serious treatment-related complications. Due to a short therapeutic window of ischemic stroke, only a small percent of stroke patients (<6%) are eligible for iv tPA treatment (Adeoye, Hornung, Khatri, & Kleindorfer, 2011; Donnan, Howells, Markus, Toni, & Davis, 2003). It has long been perceived that the severity of stroke differ from patient to patient and so does the potential treatment window. Penumbral biomarkers promise to individualize treatment windows in acute ischemic stroke. We used a novel magnetic resonance imaging approach that measures oxygen metabolic index (OMI), a parameter closely related to positron emission tomography–derived cerebral metabolic rate of oxygen utilization ($CMRO_2$), to derive a pair of ischemic thresholds: (1) an irreversible-injury threshold that differentiates ischemic core from penumbra and (2) a reversible-injury threshold that differentiates penumbra from tissue not-at-risk for infarction. This is the first paper to develop a tissue metabolic imaging biomarker to delineate ischemic penumbra tissue (An, et al., 2015). The identification of penumbra has a significant impact on selecting patients who can benefit from treatment beyond the current treatment window.

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Dr. An has had grant research support from Seimens but there is not conflict of interest.

Analyzing microvascular heterogeneity in the central nervous system: Microscopy and molecular biology join forces.

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Background – Far from being the structurally and physiologically invariant tissue once characterized, the microvascular endothelium exhibits considerable heterogeneity. This heterogeneity is classified into *segmental* and *regional*. Segmental heterogeneity refers to the phenotypic distinctions among the different tributaries of the vascular tree within any particular organ, while regional heterogeneity refers to differences in a particular vascular tributary depending on organ locale. While the blood-brain barrier (BBB) is considered to lie at the level of the brain microvasculature, the issue of heterogeneity has clouded its precise localization. Being able to accurately identify the seat of the BBB is particularly significant for better understanding mechanisms that control the flux of substances – both soluble and cellular – between the blood and brain, and for developing faithful models to aid in this investigation.

Objectives – The objectives were to exploit emerging technologies in order to resolve, qualitatively and quantitatively, differences in endothelial phenotype – anatomical and functional – along CNS microvasculature.

Methods – High-resolution, 3-D fluorescence imaging was used to analyze the distribution and relative quantification of the tight junction protein claudin-5 and infiltrating leukocytes along the different branches of the central nervous system (CNS) microvasculature. Immunohistochemistry-guided laser capture microdissection (immuno-LCM) coupled to transcription profiling was additionally used to highlight a molecular blueprint for the functional differences of the endothelium among CNS microvessels.

Conclusions – Imaging revealed an inverse correlation between the relative expression of CLN-5 and CNS microvessel diameter in the normal state, as well as the heterogeneity of functional responses of these microvessels during neuroinflammation. Additionally, imaging highlighted the step-wise progression of leukocytes across the different membrane compartments surrounding inflamed microvessels. Immuno-LCM/transcription profiling disclosed that, while CNS capillaries and venules share many BBB properties, restrictive barrier characteristics are more concentrated in capillaries while features responsible for inflammation-associated processes predominate in the venules.

Dr. Pachter has nothing to disclose nor any conflicts of interests to declare.

Non-Invasive Methods to Measure Venous Pressure and Flow Rate in Jugular by Ultrasound

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Background: The rhythmic variation of the pressure in right atrium of the heart (Dp (t)), produces a pressure waves that are transmitted from the heart to the internal jugular vein (IJV). The pressure waves interplay with blood flow in the IJV, changing both the instantaneous velocity of the blood, w (t), that the instantaneous cross sectional area, CSA (t), of such a vein [1].

Objectives: The time variation, Dp (t), of the atrial pressure, can be calculated by the equation of motion of the blood flow. This calculation is based on the quantities CSA (t) and w (t) of the IJV. With the same data one can calculate the instantaneous volumetric flow, Q (t). Similarly, if one know Dp (t) and CSA (t), it is possible to calculate the instantaneous velocity of the blood w(t).

Methods: We selected three volunteers to undergo US neck scanning. For each subject was acquired a transversal video clip of the IJV at J1 / J2 level and a Doppler trace. Simultaneously it was also acquired ECG trace.

The IJV CSA(t) was measured on the video clip as explained in [2]. The instantaneous velocity was sampled on the Doppler trace [3]. In this way, we obtained the dataset CSA_i and w_i corresponding to the CSA(t) and w (t). The two datasets were phased using the R wave of the ECG as time-marker [3]. The Navier-Stokes equations are finally used to calculate Dp(t). The instantaneous volumetric flow is calculated by integrating the CSA_i and the w_i datasets with respect to time. The flow was also calculated using the most common technique to multiply the TAV for the value of the measure of the CSA.

The speed w(t) has been calculated using the dataset CSA_i and assuming that the maximum and minimum atrial pressure (p_{max} and p_{min}) were the mean physiological age of the subject. The data set obtained was compared with the experimental dataset w_i.

Results: The Dp (t) was measured and compared with the normal range for thr age of the subject. The instantaneous flow was compared with the flow calculated by multiplying the TAV for the CSA and we found that the two values can differ up to 50%. The velocity, w_i, calculated with the equation of motion, was found to be in excellent agreement with the track Doppler acquired experimentally.

Conclusion: The proposed procedure is correct from a theoretical point of view and opens up to new perspectives for the use of US in neurological and vascular applications.

Anyway, the results presented here are not still conclusive because they miss experimental verification. Such verification can not be carried out except by invasive methods, for this reason there is surely a collective interest to deeply investigate all theoretical and practical aspects of this methodology before completing the research with appropriate experimental tests.

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Dr. Sisini has nothing to disclose nor any conflicts of interests to declare.

Evaluation of cerebral hemodynamics with microbubble enhanced ultrasound imaging and magnetic resonance imaging in MS patients

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Multiple sclerosis is the most common disease of the Cerebral nervous System that affects young adults and causes severe neurological disability. Based on strong scientific evidence it is currently considered an auto-immune organ-specific but seems unlikely to be the result of a single causal event. The disease is characterized by a profound pathological, clinical and neuroradiological heterogeneity. It 's likely that there is a single cause of disease but that it is the result of a complex interaction of factors that act with different intensity in different individuals and in different stages of the disease. Among the many factors that could determine brain damage, scientific evidences indicate ischemic changes, changes in venous outflow, accumulation of neurotoxic and pro-inflammatory substances.

Patients with MS have higher frequency of ischemic stroke and perfusion abnormalities were detected in both early and advanced stages of disease. The study of cerebral venous return is very difficult for the complex anatomical and physiological variables that come into play simultaneously. We will show the results of research carried out on patients with MS, as a model of autoimmune disease, and patients with Amytrophic Lateral Sclerosis (ALS), as a model of neurodegenerative disease, compared to a group of healthy subjects.

Moreover, we evaluated the genetic susceptibility of vascular changes in MS and ALS, using a DNA bank of the Research Unit of the Department of Neurology, Federico II University and assaying serum levels of homocysteine, prothrombotic factors, oxygen free radicals and endothelial factors (autoimmune and proangiogenetici). We also tested the association between the C677T polymorphism of methylenetetrahydrofolate reductase, and the allelic variation in two different genes responsible for the angiogenic factors VEGF-A and HIF1A and micro and macro vascular abnormalities in MS and ALS. Changes in brain arterial perfusion and transit time were studied using contrast-enhanced Perfusion-weighted MRI, while magnetic susceptibility MRI was employed to assess the state of deep cerebral venous outflow through visualization and analysis of the intracranial venous system, and to measure intracerebral iron deposits in specific locations (basal ganglia).

The morphology and haemodynamics of extracranial and intracranial vessels were evaluated using the measurement of intima-media thickness of carotid artery walls, echo-color Doppler intra-and extracranial cerebral venous district, and measurement of cerebral arterio-venous transit time with contrast-enhanced ultrasound.

The results of the ultrasound-based imaging modalities of the intra and extracranial district were compared with the alterations of cerebral perfusion and iron deposits studied with MRI and the biochemical and genetic markers of vascular risk.

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Dr. Mancini has nothing to disclose nor any conflicts of interests to declare.

The Relationship between Jugular Flow, Ventricles Volume and Brain Perfusion at SPECT-CT in CCSVI Patients.

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Objective: Chronic cerebrospinal venous insufficiency (CCSVI) is a condition characterized by restricted venous flow through the internal jugular veins and increased collateralization.[1] CCSVI was found associated to several neurodegenerative processes.

On the other hand, increased ventricles volume is an indirect index of brain atrophy, a common finding in neurodegeneration. The neurodegenerative process is also characterized by brain hypoperfusion. Moreover, in a case-control study percutaneous trans-luminal angioplasty (PTA) demonstrated to improve jugular flow and in turn cerebrospinal fluid (CSF) dynamics.[2]
We hypothesised that patients with defective jugular valves might improve CSF dynamics by surgical restore of the jugular flow.[3] An effective surgical procedure should correspond to reduced ventricle volume, so correcting a parameter of brain atrophy. In addition we measured a secondary outcome change in brain perfusion.

Methods: 56 patients (M28/F28 mean age 44±10) with Eco-Colour Doppler (ECD) screening positive for CCSVI in consequence of not mobile jugular leaflets, were further studied by means of a validated ECD flow quantification protocol,[3] MRV and SPECT-CT. Fifteen (15) patients were excluded because did not meet inclusion criteria. Twenty-seven patients (M14/F13 mean age 48±7) underwent to endophlebectomy and autologous vein patch angioplasty. Omohyoid muscle section was performed when appropriate. Finally, 14 patients matched for age and gender (M8/F6 mean age 43±11) were not treated but rechecked by at the same interval of treated patients, constituting the control group. Main outcome measures were blindly assessed, respectively ventricles volume at SPECT-CT and brain perfusion in the whole brain and in other 11 cerebral regions.

Results: in 41 patients, satisfying inclusion and exclusion criteria, jugular and collateral flow, ventricles volume and brain perfusion were measured significantly different from normal reference values. In the 14 patients who were not operated on, both ECD and SPECT-CT did not show significant changes at follow-up. To the contrary, in the operated group, the collateral outflow from the brain respect to the arterial inflow passed from 62% to 21% ($p<0.0001$), thanks to improved flow through the internal jugular vein. Correspondingly, ventricles volume dramatically decreased (from 33.2 ± 13.8 mm^3 to 30.8± 13.6 mm^3; $p< 0.0025$), clearly suggesting a reduced cerebrospinal fluid re-absorption in CCSVI condition, which was corrected by extra-cranial venous surgery.
In addition, perfusion was found improved in the surgical cohort respect to controls ($p<0.017$).

Conclusion: to fix the restricted flow through the main brain outflow routes, in CCSVI cases,

(Menegatti, cont'd)

significantly reduces ventricles volume and improves cerebral perfusion, both representing common features in several neurodegenerative disorders.

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None of the authors have anything to disclose nor any conflicts of interests to declare.

Cerebral venous drainage and its impact on cerebrospinal fluid motion: a retrospective review of the work of the ISNVD

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Since the inception of the Society, members of the ISNVD have pioneered work on the interaction between the cerebrospinal fluid (CSF) system and the cerebral venous drainage system, and its possible involvement in neurological disease. Initial investigations by ISNVD members involved the association between multiple sclerosis (MS) and increased CSF pulsatility in the Aqueduct of Sylvius (AoS) [1,2]. This was followed by a study that reported a similar phenomenon in healthy adults without neurologic disease [3], suggesting that increased aqueductal pulsatility might be primarily due to altered intracranial biomechanics associated with constricted cerebral venous drainage, rather than neuronal decay. This opinion was reinforced by Zivadinov et al., [4] who performed venous angioplasty on MS patients diagnosed with chronic cerebrospinal venous insufficiency (CCSVI) and found that the procedure normalized CSF pulsatility in the AoS. Independent work by Zamboni and co-workers [5] had already shown a 63% increase in the hydraulic resistance of the extracranial venous pathways in MS patients diagnosed with CCSVI [6]. As such, this body of work indicated a direct biomechanical link between cerebral venous outflow and the motion of the CSF pulse in the AoS, a link that was later confirmed by Lagana, Beggs and co-workers in a MRI study that demonstrated a strong positive correlation ($r=0.966$, $P<0.001$) between the intracranial venous blood volume and the aqueductal CSF volume in healthy young adults [7].

Although the clinical implications of this work are yet to be fully understood, increased CSF pulsatility in the AoS has been associated with early stage white matter damage (WM) in healthy individuals without neurologic disease [8]. As such, this appears to support the work of Chung et al [9], who found jugular venous reflux (JVR) to be associated with more severe age-related WM changes in the elderly. Collaborative work between Chung, Zivadinov, Beggs and there co-workers also revealed JVR to be associated with intracranial structural changes in Alzheimer's disease patients, which resulted in increased gray matter volume [10]. This unexpected finding, which has since been mirrored in a subsequent study investigating aging in healthy individuals [11], suggests that venous drainage anomalies may have far reaching neurological implications, leading to increased venous blood retention in the cranium, something that has the potential to alter the dynamics of the intracranial CSF system.

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Dr. Beggs has nothing to disclose nor any conflicts of interests to declare.

Origin and Clinical Relevance of the Cranio-Spinal CSF pulsation

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MR imaging of the cerebrospinal fluid (CSF) flow dynamics is becoming an integral part of many clinical exams. Therefore, understanding the CSF flow dynamic is critical for successful utilization of CSF flow studies for diagnosis and treatment decisions of related brain disorders. The two most commonly measured CSF pulsations are the CSF flow through the aqueduct and the CSF pulsation between the cranium and the spinal canal, i.e., the cranio-spinal CSF pulsation. These two types of CSF pulsations provide distinctly different information about the cranio-spinal system. This presentation reviews progress made over the years in identifying the driving force and the modulators of the cranio-spinal CSF pulsation and the means by which the cranio-spinal CSF pulsation can be used for derivation of key cranio-spinal biomechanical properties such as intracranial compliance and pressure.
The CSF flow dynamics is influenced by two separate processes; the circulation of the CSF from its formation sites to its absorption sites (i.e., bulk flow), and an oscillatory (back and forth) flow during the cardiac cycle (pulsatile flow). The first process governs the overall volume of CSF in the craniospinal space and thereby influences intracranial pressure (ICP). The second process, the oscillatory movement of the CSF within the craniospinal compartments, is caused by the pulsatile blood flow entering and leaving the intracranial compartment during the cardiac cycle. These two processes occur over different time scales. The circulation and replenishing of CSF in the craniospinal system occurs over minutes while the time scale of the pulsatile CSF flow is milliseconds.

A system modeling approach and accounting for volumetric flow rates to and from the cranium provided the first evidence that cranio-spinal CSF pulsation is driven by the net trans-cranial blood flow, i.e., arterial inflow minus venous outflow, and is modulated by the cranio-spinal intracranial compliance [1]. This has been further confirmed by direct estimation of the intracranial compliance from the ratio of the volume and pressure changes that occur with every heart beat [2, 3]. Early experience of MR measurements of intracranial compliance and pressure (MRICP) from several centers and the added value for basic research and clinical applications will be reported.

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About the Presenter. Noam Alperin is a professor of Radiology and Biomedical Engineering at the University of Miami, where he is heading the Physiologic Imaging and Modeling lab (PIML). Research areas include brain biomechanics, cerebral blood and CSF flow dynamics, and quantitative morphology. Dr. Alperin is a shareholder in Alperin Noninvasive Diagnostics Inc. and owns the rights for the MRICP patent.

Cerebrospinal fluid and control of intracranial pressure

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Until the recent past (2010) the accepted classification of hydrocephalus had been the one proposed by Walter Dandy of Johns Hopkins in 1913. This classification was based on autopsy material and dye studies in which methylene blue was injected into the ventricles of animals and later of humans and spinal fluid was retrieved from the lumbar theca. From these observations he postulated that hydrocephalus was either **communicating** (dye was recovered) or **non-communicating or obstructive** (no dye). Based on this classification Dandy began treating the communicating patients with choroid plexectomy and obstructive hydrocephalus with third ventriculostomy originally done by the removal of one optic nerve.[4]

With the findings based on research, clinical outcomes, technology and especially on neuroimaging that are available at this time it was clear that this classification from over a century ago was out of date. A group of neuroscientists and neurobiologists came together to produce a new classification that would be beneficial for clinical use as basic science research. As presented at the Fifth International Hydrocephalus Workshop held in 2010 on the Island of Rhodes this classification was based on the point of obstruction of flow of CSF from the point of production in the cerebral ventricles to the point of absorption into the systemic circulation.[6] The participants are shown as an appendix to this summary.

Determining the point of restriction of flow of CSF gives the clinician an idea of what the potential types of intervention are that can result in positive treatment outcomes and the basic scientist can fully understand the importance of the findings and whether or not it is generalizable to multiple types of hydrocephalus. It also leads to limiting the potential causes simplifying the differential diagnosis. This paradigm can also explain all abnormalities of CSF dynamics including Idiopathic Intracranial hypertension (IIH) and its analogy "severe slit ventricle syndrome" (SSS).[2,5] SSS relates to a subset of patients who, when the shunt originally placed for hydrocephalus, fails the ventricles do not enlarge and therefore the diagnosis is often missed. Both of these have been shown to be due to venous hypertension .[2] Uniquely in babies hydrocephalus can result exclusively from venous restriction of flow and has even been successfully treated with a bypass from the transverse sinus to the jugular vein. [8] The causes and possible treatments of IIH and SSS continue to remain controversial. The restriction of flow of CSF particularly in the transverse sinus has been shown to decrease if the intracranial pressure is artificially lowered as by doing a lumbar puncture leading some to conjecture that stenting is treating the effect and not the cause.[9] Confirmation is growing that, at least part of the rise in the intracranial pressure is due to restriction of flow in the dural venous sinuses and that stenting of these reversible constrictions can lead to lowering of overall ICP.[10]

There is a heated discussion regarding the role of modification of the modest bulk flow of CSF and its pulsatile nature as explanation for ventricular distention in hydrocephalus. These two forces must work together for the ventricles to expand. CSF turnover is approximately 0.3 cc/minute and therefore very little energy is generated for the distention of the ventricles. Augmentation of the pulsatile component of the intracranial system has been shown to lead to increases in ventricular volume in experimental animals.[1] Despite a great deal of commitment to this concept there has been no naturally occurring model of amplified pulse wave causing hydrocephalus and to this point no damping of the pulse wave

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has led to moderation in ventricular volume. The primary problem in naturally occurring hydrocephalus requires that the absorptive capacity or flow rate be restricted in order to enlarge the ventricles whether that restriction of flow is within the CSF compartment or in the venous outflow or related to marked increase in the volume of CSF produced.[7] The amplitude of the pulse wave depends on the volume of distribution of volume added whether it be by cardiac waves, respiratory waved, transient pulses such as coughing or valsalva maneuvers or by addition of mass to the intracranial pressure. The smaller the volume that the central nervous system inhabits the larger the pulse amplitude and the greater the energy available to lead to ventricular expansion.

Conclusion:

Normal intracranial cerebrospinal fluid pressure dynamics are characterized by the following conditions

1. The preponderance of CSF production occurs within the cerebral ventricles by either transependymal flow from brain extracellular fluid or from active secretion by the choroid plexuses
2. All CSF is in communication from ventricles to spinal and cortical subarachnoid spaces
3. While there are certainly a variety of pathways to CSF absorption in order to prevent abnormal ventricular distention it is essential for the CSF to gain access to the cortical subarachnoid space.[3]
4. Until intracranial pressure rises to such an extent that it interferes with cerebral perfusion, brain (and for that matter spinal cord in syringomyelia) dysfunction does not occur as a result of changes in pressure but requires distortion of the structure (i.e. distortion of the brain or cerebral edema).

Appendix

Members of the Hydrocephalus Classification Study Group

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Dr. Rekate has nothing to disclose nor any conflicts of interests to declare.

NPH, pseudotumor cerebri, leukoaraiosis and pulsewave encephalopathy

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Normal pressure hydrocephalus (NPH) presents with a disturbance of gait, cognitive impairment and urinary incontinence. Imaging shows enlarged ventricles despite the CSF pressure being within the normal range. MRI imaging shows an elevation in the volume and velocity of the CSF passing through the aqueduct, with the timing of the flow being closely correlated to the heart beat. The hyperdynamic flow through the aqueduct in NPH could theoretically be due to either an increase in the expansion of the arteries within and around the brain or a failure of dampening of this pulse. Pulse wave dampening is achieved by either displacing CSF from the cranial cavity into the spinal canal or compressing the cortical veins and expelling blood into the venous sinuses. Measurement of the arterial pulse volume has shown it to be normal in NPH but the pulse wave velocity within the vessels of the brain is twice normal [1]. Seventy percent of the capacitance is on the venous side of the vascular tree and venous compression is a large component of pulse wave dampening. Therefore, a significant reduction in venous compliance is the cause of the hyperdynamic flow in NPH due to a failure of pulsation dampening.

Leukoaraiosis is a patchy demyelination of the cerebral white matter due to degeneration of the oligodendrocytes. Alzheimer's disease is loss of grey matter, associated with amyloid deposition in the microvessels. Both of these conditions are over represented in patients with NPH. Vascular risk factors are highly associated with all of these conditions but pure ischemia correlates poorly with both early leukoaraiosis and Alzheimer's disease. Despite the mean blood flow not correlating with these conditions, measures of pulsation strength do correlate with early disease [2,3]. This finding suggests that alterations in pulse wave dampening may be associated with both of these conditions.
Pulse wave encephalopathy is a concept whereby a failure of dampening of the arterial pulse pressure within the arteries and arterioles of the brain, due either to an increase in the pulse pressure or a failure of the dampening mechanism, leads to increased wall stress within the capillary bed [4]. Opening of the blood brain barrier leads to increased interstitial water and increased mechanical stress to the neurones and oligodendrocytes surrounding the capillaries could largely account for the pathological findings in many apparently degenerative cerebral diseases.

In many ways, pseudotumor cerebri is the antithesis of NPH. Unlike NPH, there is an elevation in CSF pressure above the normal range but the ventricles remain small. In addition the flow of CSF through the aqueduct is not increased and thus pulse wave dampening is not affected. It has been shown that all patients have an increase in venous sinus pressure. This pressure increase comes about by a combination of an elevation in central venous pressure (due to obesity), venous outflow stenosis (venous collapse and a positive feedback effect) and a reflex increase in cerebral blood flow brought about by the alteration in the cerebral metabolism [5].

The author declares no conflict of interest or disclosures in the material presented.

5 years experience of CCSVI endovascular treatment of a cardiologist

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There are more and more published data showing CCSVI as an atomical pathological condition is a predisposing factor for neurodegenerative diseases such as MS, Migraine, Parkinson disease, LAS, Alzheimer and others.

We present our 5 year experience of endovascular treatment of CCSVI.

Patients and methods:

In our registry between January 2010 and February of 2015 we included 1232 patients (765 women, 467men, at average age 49.3 years) with above mentioned diseases and positive for CCSVI by Doppler examination.

Before the interventional procedure CCSVI condition was confirmed with venous or arterial angiograpfhy showing narrowing and/ or slow flow, stagnation, reflux in 97% (1196) of the patients with positive Doppler criteria. In angiographically positive patients we applied endovascular treatment of both jugular and azigous veins using predominantly balloon angioplasty (balloon size from 5 to 18mm, mean inflation time 117 sec) and in just several cases (18, 1.5%) additional stenting. In hospital MAE (death, major bleeding, clinical deterioration, and surgical conversion) was 0%. Average hospital stay was 1.77 days. All the patients were followed clinically and by Doppler at least for 6 months. Immediate clinical improvement was seen in 78% of the patients with reduction of such symptoms like incontinence, headache, balance disorders, sexual disfunction, blurriness of vision. In the MS group the mean EDSS drop from 7.7 to 5.5. In 178 patients we examined the blood gaz change and have shown on top of the flow improvement significant improvement in the oxygenation, saturation and hypercapnia after the angioplasty. In the follow-up we have observed restenosis rate of 37%, stady state in the clinical condition in 56%, additional improvement in 23% and mild deterioration in 21%. In all patients with clinical worsening was established restenosis.

Conclusions:
The endovascular treatment of CCSVI are extremely safe and efficient regarding restoration of impaired venous flow. The successful blood flow restoration is leading to clinical improvement in majority of cases. We need late vascular result optimization because the clinical result seems to be correlated with the vascular patency durability.

Dr. Petrov has nothing to disclose nor any conflicts of interests to declare.

Factors influencing the efficacy of balloon angioplasty in the treatment of outflow anomalies of Internal Jugular Veins

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Purpose: To investigate the efficacy of balloon angioplasty in the treatment of outflow abnormalities of Internal Jugular Veins (IJVs).

Materials and Methods: A total of 996 consecutive patients with venous outflow anomalies underwent balloon angioplasty of the IJVs. In all patients was performed the same examiner-independent catheter venography protocol in the aim to determine the variations of occlusive IJVs disease and delay flow status pre and post PTA. In order to ensure consistency to statistical analysis, patients who: had preview thrombosis or stent; were treated on one side but not the other; or whose data was corrupted, were excluded, leaving a final study dataset of 797 patients. In this study were evaluated different factors as: Contrast medium clearance pre and post PTA, features of endoluminal defects, presence of hypoplasia and extrinsic compression and age.

Statistical Analysis:Univariate analysis was performed on the left and right IJVs separately, with all 797 subjects grouped together. Pre and post-PTA differences in IJV flow were tested using a two-tailed Mann-Whitney U-test, while changes in the stenosis status were evaluated using a chi-square test. P values <0.05 were deemed to be significant. In order to gain deeper insights into the impact of PTA on IJV flow, scatter plots were produced for the left and right IJVs to assess the effect of the intervention on the entire study population (n = 797). In order to identify which variables could be used to predict the success or failure of PTA, logistic regression analysis was performed using the clinical sub-group variables plus age and pre-PTA flow.

Results:The univariate analysis reveals strongly significant changes ($p<0.001$) in both IJV flow and stenosis status before and after the intervention. With the exception of hypoplasia, which was occurred more in the left IJV ($p<0.001$), no significant differences were observed between the left and right IJVs for the other clinical variables. The PTA intervention had an effect on the flow rates in a sizable proportion of the patients. This effect was significant for pre-PTA values >12 frames. However while the effect was significant, it is noticeable that the intervention failed to improve the IJV flow rate in a substantial number of subjects. This phenomenon was observed for both the right and left IJVs. Analysis of the pre and post-PTA IJV flows rates for the various clinical sub-groups reveals that with the exception of the hypoplasia positive patients, significant differences (or statistical trends i.e. $p<0.1$) were observed for all the clinical sub-groups. Having said this, the data also reveals that for most sub-groups the impact of the PTA was relatively modest (Cohen's $d<0.4$). The one major exception to this, was in those patients with a transversal endoluminal defect, in whom the intervention of PTA had a large effect (Cohen's $d>1.1$).We also divided the patients into two outcome groups: those who's IJV blood flow improved after PTA; and those who did not improve. From this it can be seen that the subjects who improved were younger than those who did not. Also, the improvers had less longitudinal endoluminal defects and more transversal defects, and tended to suffer less from hypoplasia.

The results of logistic regression analysis reveals, for both the right and left IJVs, the presence of transversal endothelial defects is the single most important criteria for determining whether or not PTA

will be successful. While transversal endoluminal defects have a positive coefficient, all the other variables in the models have negative coefficients, implying opposite effects. Collectively, this suggests that younger individuals with transversal endoluminal defects and higher pre-PTA flows are more likely to respond well to PTA compared with those who exhibit hypoplasia, stenosis or longitudinal endoluminal defects.

Conclusions: The results of the study present a clear and consistent picture, namely that PTA does have an effect on IJV blood flow. However, this effect is not homogeneous, with PTA being more successful in some clinical sub-groups than others. In particular, PTA appears to be more effective in younger individuals, with transversal endoluminal defects and an absence of hypoplasia or longitudinal endoluminal defects.

None of the authors have anything to disclose nor any conflicts of interests to declare.

CCSVI Tracking: The Dutch database.

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Introduction:

The "CCSVI Tracking" is a data compilation created by an independent group of volunteers, most of them patients with multiple sclerosis (MS). Most of these volunteers have undergone venous angioplasty for CCSVI treatment and have entered the information electronically into a database that was created by the group. CCSVI Tracking is an independent group and has no relationship with specialists or industry. The electronic access site has been open to participants since August 17 of 2010. Physicians did not collect the information in the database; it was entered by the patients based on their experience with the procedures and the outcomes as interpreted by them.

Participants and Treatments:

According to the updated version, there are 919 registered participants, who have undergone 751 treatments. Most of the registered participants are from Canada (40%), United States (30%), the Netherlands (20%) and the United Kingdom. Patients from an additional 16 countries are also included. Treatments were mainly rendered in the United States (45%), Poland (20%), Belgium, Germany, Mexico and Bulgaria.

Treated veins included: Left jugular vein (42%), right internal jugular vein (37%), azygos vein (18%). Other treated veins included iliac, lumbar, vertebral, and brachiocephalic veins.
Patients describe that the most common treated abnormalities included stenotic vein walls, unknown conditions, pathologic valves, and hypoplastic valves.
The most common intervention conducted was balloon angioplasty (90%). Other endovascular treatments included the use of cutting balloon, stent placement, laser, anticoagulation only, and open surgery (less than 5% each). Most patients have undergone only one treatment (90%), with only a few undergoing 2 treatment sessions and a minimal percentage of patients undergoing three treatments or more.

Outcomes:

Based on the information rendered in aggregated graphs, 40% of patients reported significant improvement in overall symptoms, 20 % mild improvement, 25% no change and approximately 15% mild or severe worsening of symptoms. Regarding the EDSS scores, 40% reported stability of their starting score, 20% a mild improvement, 20% a significant improvement, and 20% worsening. The symptoms that improved the most after treatment included: coordination, muscle control, bladder and bowel function, cognitive function, brain fog, dizziness and fatigue. No complications or deaths are reported and this information is difficult to retrieve from the database.

Conclusion:

The CCSVI tracking is a large database obtained from a total of 751 treatments for CCSVI. Overall results are comparable to what has been previously reported. Unfortunately information regarding

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complications and deaths is not readily available. Publication of the information in this database would be useful, however, further research and updating of the information will be necessary to achieve this goal.

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Acknowledgement:
I would like to thank Margreet Sienstra and the CCSVI tracking developers for allowing me to access the site and retrieve the necessary information for this presentation.

Disclosure:
I am a consultant for Terumo and WL Gore. Products from these companies will not be mentioned during this presentation.

Reasons for Failure in Neurovenous Interventions

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Patients with neurodegenerative diseases, notably multiple sclerosis (MS), have a propensity to venous outflow obstructions of the cerebrospinal venous circulation and that treatment may rapidly show dramatic clinical improvements. Rapid improvements suggest that they are likely related to altering cerebral fluid dynamics, such as enhanced cerebral perfusion, increased dural venous flow and improved CSF drainage rather than reversal of basic pathology.

However, not all patients realize clinical improvements and the benefits seen in other patients may be transient and short-lived. Further, disease may progress despite persistence of benefits. There are many reasons for poor clinical results after angioplasty. Broadly speaking, they can be divided into issues related to the nature of neurodegenerative disease with persistent inflammation and clinical relapse, to technical and cognitive issues related to the treatment of vascular obstructions, including failed or incomplete diagnostic evaluations, incomplete, inadequate or erroneous therapeutic efforts, to inherent problems with trans-catheter treatments, such as angioplasty injury, restenosis and occlusion, and to inability or failure to provide adequate follow-up after treatments.

These concepts will be illustrated using case material acquired from review of failed treatments for the past five years.

To summarize, non-responders either have no improvements, have un-sustained improvements, have worsening symptoms and disease relapses or develop deteriorations resulting from complications. Some of this is inevitable. Attention to the details of therapy can increase clinical response in some patients. Discussing this topic with patients before treatment helps patient develop realistic expectations about the outcomes of angioplasty.

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Dr. Sclafani has no disclosures to make or conflicts of interests to declare.

High-Throughput Endothelial Models of Flow and Shear: Effects of pulsatile and non-laminar fluid shear stresses

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Deviations from normal levels and patterns of vascular fluid shear play important roles in normal physiology and pathophysiology by inducing adaptive as well as pathological changes in endothelial phenotype and gene expression. In particular, effects of non-laminar, pulsatile flow induced shear stress can cause a variety of effects on certain cell types. While by now many endothelial cells from diverse anatomic origins have been cultured, in depth analyses of their responses to fluid shear have been hampered by the relative complexity of shear models (e.g. parallel plate flow chamber, cone and plate flow model.) While excellent approaches, these models are technically complex and suffer from drawbacks including relatively lengthy and complex setup time, low surface areas, requirements for pumps and pressurization often requiring sealants and gaskets representing challenges to sterility and often low n-values. If higher throughput models of flow and shear were available, more rapid progress in vascular endothelial shear response research at the molecular level might be more rapidly advanced. Here, we describe the construction and use of shear rings, a novel, simple to construct, inexpensive model for studying laminar and turbulent shear which permits relatively high n-values and high surface areas.

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Progress towards a global circulation mathematical model, incorporating detailed CSF and lymphatics dynamics

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The biophysics of complex and strongly interacting fluid systems in the central nervous system, and the rest of the body, appears to play a crucial role in the understanding of underlying mechanisms at the root of neurodegenerative diseases [1].

Here we first describe a global mathematical model for the systemic circulation, coupled to a refined sub-model for the cerebrospinal fluid system that extend the works [2]-[4]. We show simulation examples of the impact of extracranial venous strictures on cerebral venous and CSF dynamics.

We then speculate on the physiological implications for studying neurodegenerative diseases of the glymphatic system [5], the newly discovered brain lymphatic system [6], [7] and their coupling to other fluid systems. We finish by describing current progress towards the construction of an all-fluids global mathematical model and discuss the challenges posed.

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Dr. Toro has no disclosures to make or conflicts of interests to declare.

Structural Changes in Extra-CNS Blood Vessels in Neurodegeneration

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Venous abnormalities have been associated with different neurological conditions and the presence of a vascular involvement in multiple sclerosis (MS) has long been anticipated. In view of the recent debate regarding the existence of cerebral venous outflow impairment in MS due to abnormalities of the azygos or internal jugular veins (IJVs; *Zamboni et al,. J Neurol Neurosurg Psychiatry, 2009; 80:392-399)*, we have studied the morphological and biological features of IJVs in MS patients *(Coen et al., Cardiovasc Pathol, 2013, 22:33-38).*

We had the opportunity to investigate the histological features of vein specimens (provided by the Vascular Diseases Center and the Operative Unit of Vascular and Endovascular Surgery, S. Anna University-Hospital, Ferrara, Italy and by the Division of Clinical Pathology, Geneva University Hospitals, Geneva, Switzerland). We examined: 1) IJVs specimens from MS patients who underwent surgical reconstruction of the IJV and specimens of the great saphenous vein used for surgical reconstruction; 2) different vein specimens from a MS patient dead of an unrelated cause; and 3) autoptical and surgical IJV specimens from patients without MS. Collagen deposition was assessed by means of Sirius red staining followed by polarized light examination. The expression of collagen type I and III, cytoskeletal proteins (α-smooth muscle actin and smooth muscle myosin heavy chains), inflammatory markers (CD_3 and CD68) were investigated.

Our results showed that the extracranial veins of MS patients exhibited focal thickenings of the wall characterized by a prevailing yellow-green birefringence (corresponding to thin, loosely packed collagen fibers) correlated to a higher expression of type III collagen. No differences in cytoskeletal protein and inflammatory marker expression were observed.

The IJVs of MS patients presenting a focal thickening of the vein wall are characterized by the prevalence of loosely packed type III collagen fibers, i.e. an altered collagen type I/III ratio, in the adventitia; this ratio is similar to that observed in fibrotic lesions but without the presence of myofibroblasts. The absence of inflammatory cells within the vein wall lesions suggests that the altered collagen I/III ratio is not secondary to an inflammatory disorder.

Our results establish for the first time a morphological and biological description of extracranial vein alteration in MS. These findings could account for the flow abnormalities occasionally described in MS. Further studies are required to determine whether the observed venous alterations play a role in MS pathogenesis.

Dr. Bochaton-Piallat has no disclosures to make or conflicts of interests to declare.

5 SUBMITTED ABSTRACTS – PODIUM

Longitudinal Magnetic Resonance Imaging of Cerebral Microbleeds in Multiple Sclerosis Patients

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Background: Cerebral Microbleeds (CMBs) have been associated with dementia, traumatic brain injury, and aging. Susceptibility weighted imaging (SWI) and quantitative susceptibility mapping (SWIM) offer sensitive methods to detect CMBs.

Objectives: The prevalence of CMBs in Multiple Sclerosis (MS) patients is sought to better understand neurovascular complications in this disease. Using SWI and SWIM, we study CMBs longitudinally in a cohort of MS patients.

Methods: Magnetic resonance imaging (MRI) was performed on 50 MS subjects (40RR, 8SP, 2PP: 19 male, 31 female) aged 45.8+/-11 years (27 younger than 50 years) at baseline with a 2 year follow-up. Disease duration was 12.8+/-9 years. EDSS was 3.0+/-2 for baseline and 3.1+/-2 for follow up. SWI was collected with raw phase data saved (TR=40ms, TE=21ms, 0.5x0.5x2.0mm^3) and SWIM data were calculated[1]. Conventional MRI sequences were acquired. CMBs were identified from simultaneously viewing magnitude, phase, SWI, and SWIM slices to differentiate potential mimics as well as their projections in MPR to determine connectivity with surrounding structures.

Results: Nine (18%) subjects had CMB at baseline and an additional two subjects without CMBs initially developed CMB at the two year follow up (22%). Both subjects who had developed CMB after 2 years were younger than 50 years (19 and 38 years respectively) and their EDSS remained stable. Two subjects had CMB present at baseline, 2 and 3 CMBs were observed, and in the follow up scan 3 and 5 CMBs were observed, respectively. Absolute and change in EDSS scores did not correlate with CMB prevalence or development for the cohort. If subjects younger than 50 are separated, 15% (4/27) younger than 50 years had CMBs at follow-up and 30% (7/23) 50 years or older had CMBs at follow-up.

Conclusion: Previous literature suggests that for younger healthy individuals the prevalence of CMB is low (1.3%) while older individuals show increasing prevalence after 50 (10.7%), 60 (17.6%), and 70 (23.6%) years of age[2]. This study suggests that MS patients may have higher prevalence of CMBs than healthy controls; however case-control studies are needed to confirm that.

Keywords: Multiple Sclerosis, Cerebral Microbleeds, Susceptibility Weighted Imaging

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Arterial Pulse Pressure Waves Causing Endothelium And Myelin Damage May be A Causal Factor In Multiple Sclerosis

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Background: Mechanical deformation of myelin and endothelium can result in cell damage that initiates inflammation. Inflamed vessels release chemokines/cytokines that activate immune cells allowing CNS infiltration of immune cells. If such infiltrating cells recognize myelin antigens as foreign an immune response is initiated resulting in MS lesions.

Mechanical damage of microvessels and adjacent myelin can occur if arterial pulse pressure waves are not dissipated before reaching the microvasculature. This force dissipation results from the elastic expansion of the arterial walls absorbing some of the force and by the increased resistance of the branching arterial tree. The cranium being a rigid bony box can only allow expansion of arteries during systole if there is displacement of cerebrospinal fluid (CSF) and/or venous blood. A number of studies have shown that CSF flow through the cerebral aqueduct has a larger volume and greater velocity in MS patients than in healthy controls: this can only be due to more of the arterial pulse pressure force penetrating deeper than normal resulting in more of the force being exerted onto the ventricular CSF[1], as well as onto myelin and endothelium.

Both the stiffness of the arteries and how readily venous blood is displaced influence the pulse pressure wave dissipation. Studies have shown that MS patients generally have stiffer arteries than matched controls[2] and many have obstructed venous return[3,4]. Obstruction of the venous return reduces the ability of arteries to dissipate the pulse pressure force[5] whereas venous angioplasty ameliorates MS symptoms[6].

Conclusions: To treat MS it is critical to understand what causes the initial damage to endothelium and myelin. Are pulse pressure forces involved? It is important to know what proportion of MS patients have problems with arterial pulse pressure wave dissipation; and of those, which have obstructed venous return, increased stiffness of arteries or a combination[7].

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Dr. Juurlink has no disclosures to make or conflicts of interests to declare.

Cerebral Microbleeds in Multiple Sclerosis. A Case-Control Study

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Purpose: Cerebral microbleeds (CMBs) are associated with aging and neurodegenerative disorders. No previous studies investigated prevalence of CMBs in multiple sclerosis (MS).

Objectives: To assess prevalence of CMBs in MS and clinically isolated syndrome (CIS) patients and explore their association with clinical outcomes.

Methods: This prospective study was approved by Institutional Review Board and subjects gave their informed consent. 445 MS patients (283 relapsing-remitting, 120 secondary-progressive and 41 primary-progressive), 45 CIS patients, 51 patients with other neurologic diseases (OND) and 177 healthy controls (HCs) were assessed by 3T MRI and clinical examinations. A subset of 168 MS patients and 50 HCs underwent neuropsychological testing. CMB number was assessed on susceptibility-weighted images using Microbleed Anatomical Rating Scale, while volume was calculated using quantitative susceptibility maps.

Results: Significantly more MS patients had CMBs compared to HCs (19.8% vs. 7.4%, p=0.01) in ≥50 years old age group. Compared to HCs, a trend for greater presence of CMBs was found in MS patients (p=0.016), and in CIS patients <50 years old (p=0.039). In regression analysis, adjusted for demographic, cardiovascular risks and MRI (T2 lesion and whole brain volumes) variables, increased number of CMBs was significantly associated with increased physical disability in MS population (R^2=0.23, p<0.0001). In correlation analysis, increased number of CMBs was significantly associated with deteriorated auditory/verbal learning and memory (p=0.006), and there was a trend for visual information-processing speed p=0.049), in MS patients.

Conclusions: Monitoring CMBs is relevant in MS and CIS patients at higher risk for developing cognitive and physical disability.

Key words: multiple sclerosis, cerebral micorbleeds, prevalence, disability, cognition

Study disclosure:
This study was funded with internal resources of the Buffalo Neuroimaging Analysis Center. In addition, we received support from the Jacquemin Family Foundation.

(Zivadinov, cont'd)

Financial Relationships/Potential Conflicts of Interest:

Robert Zivadinov received personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health and Novartis for speaking and consultant fees. He received financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin-Coherus and IMS Health.

Deepa P. Ramasamay, Paul Polak, Jesper Hagemeier, Christopher Magnano, Niels Bergsland, Nicola Bertolino and Ferdinand Schweser have nothing to disclose.

Michael G. Dwyer has received consultant fees from Claret Medical and EMD Serono.

Bianca Weinstock- Guttman received honoraria as a speaker and as a consultant for Biogen Idec, Teva Pharmaceuticals, EMD Serono, Genzyme&Sanofi, Novartis and Acorda. Dr Weinstock-Guttman received research funds from Biogen Idec, Teva Pharmaceuticals,, EMD Serono, Genzyme&Sanofi, Novartis, Acorda.

Channa Kolb has received speaker honoraria from Novartis, Genzyme and Biogen-Idec.
Ralph RH.. Benedict has acted as a consultant or scientific advisory board member for Bayer, Biogen Idec, Actelion, and Novartis. He receives royalties from Psychological Assessment Resources, Inc. He has received financial support for research activities from Shire Pharmaceuticals, Accorda and Biogen Idec.

David Hojnacki has received speaker honoraria and consultant fees from Biogen Idec, Teva Pharmaceutical Industries Ltd., EMD Serono, Pfizer Inc, and Novartis.
Mark E. Haacke is the president of Magnetic Resonance Innovations, Inc.

Designing Novel Imaging Probes for Targeting Inflammatory Lesions in Brain Disorders

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Inflammation is central to maintaining a functional, healthy state within a host system. However, dysregulation of the inflammatory response results in tissue damage and chronic activation is associated with a variety of pathological conditions, particularly within the brain. Mechanisms of pathology are often poorly understood and in order to address clinical issues and improve therapeutic tools, visualisation of the inflammatory process on a molecular and cellular level is crucial.

During the biological signalling cascade associated with immune activation, neutrophils are recruited to inflammatory foci and their surface formyl peptide receptors 1 and 2 (termed FPR1 and FPR2) can be targeted as inflammatory markers.[1] This project aims to design, construct and test novel, versatile, targeted imaging probes that can specifically bind to FPRs and provide a means to directly observe and mechanistically probe the physiological process of inflammation.

In this project, several synthetic strategies have been employed to prepare targeting moieties (both peptide and small molecule, using cFLFLFK and Quin C7 vectors)[2, 3-7] which are combined with DOTA-based ligand scaffolds that are available for binding Gallium (for PET or SPECT imaging via ^{68}Ga or ^{67}Ga respectively), or lanthanides that offer MRI signals (Gd) and optical imaging (typically Eu or Tb). The resulting selective probes present an adaptable approach towards clinically relevant, diagnostic imaging of neuroinflammatory sites and will be carried forward for *in vitro* validation and, further along the line, *in vivo* testing on relevant models of inflammation.

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Keywords: formyl peptide receptors, inflammation targeting, molecular imaging

The authors have no disclosures to make or conflicts of interests to declare.

Introducing the next generation of microvascular imaging with a new USPIO-enhanced MRAV approach

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Background

Microvascular or small vessel abnormalities have been increasingly identified as the basis of many neurovascular/neurodegenerative disorders[1]. Imaging the cerebral venous system is currently achieved using susceptibility weighting imaging (SWI)[2,3]. However, SWI is unable to image arteries since there is a susceptibility matching with the surrounding tissue due mostly to the lack of deoxygenated hemoglobin in the arterial system. This study was to test whether both the arterial and venous systems could be detected on ultra-high-resolution MR arteriograms and venograms (MRAV) with the injection of an ultrasmall-superparamagentic-iron-oxide (USPIO), a negative blood pool contrast agent.

Methods

Pre- and post-USPIO (Ferumoxytol, 2 mgFe/kg) SWI was performed in a healthy volunteer on 7T MR. In order to obtain ultra-high resolution images (0.11x0.11x1.25mm), an asymmetric gradient-echo was acquired with the following image parameters: TR = 35ms, TE1 = 8ms, TE2 = 16ms and flip angle = 10° for a 13 min acquisition time for each echo. SWI data were processed using a high-pass filter with a 96x96 kernel since we were interested only in the small structures, i.e., the vessels.

Results

The visibility of the arterial systems of the basal ganglia and cerebellum has been largely improved as well as the periventricular area (Fig.1). USPIO-enhanced-MRAV not only enhances the venous system, but remarkably also the arterial system. Exploiting the flow effect at short echo time (8ms), pre-USPIO MRAV maximal intensity projection allows arterial vasculature reconstruction pre-contrast (Fig.1-A). Small arterial blooming is also seen on post contrast MRAV, more prominent at longer TE (Fig.1-D TE=16ms) than low TE (Fig.1-C TE=8ms). Small arteries (diameter=200~400μm) were seen 1.5~2 times bigger on post-contrast MRAV with TE=16ms (Fig.1-D). On the MRAV mIP images post-contrast, cortical arteries are seen parallel to veins.

Conclusion

We have demonstrated the feasibility to generate ultra-high-resolution MR MRAV using USPIO-enhanced SWI, which can be a powerful tool in detecting microvascular abnormalities that are not available on conventional MRI angiograms.

Figures:

(Brisset, Cont'd)

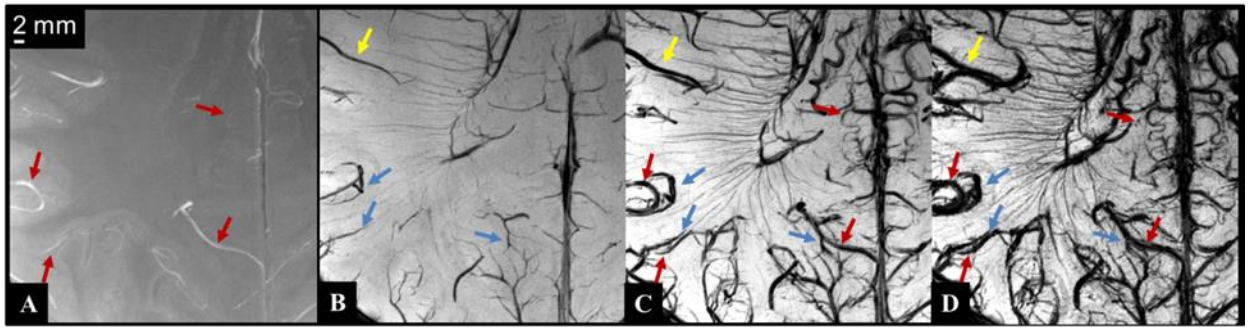

Fig.1: Pre-contrast MIP SWI (TE=8ms) (A) shows arteries due to the time of flight effect. Pre-contrast minIP SWI (B) shows veins due to stronger susceptibility of deoxyhemoglobin but no arteries. Post-Ferumoxytol (2mg/kg) SWI (C) shows both veins (blue arrows) and arteries (red arrows). With the blooming effect, the vessels appear bigger on the images post-contrast (yellow arrows) at TE=8ms (C) and even larger at higher TE = 16ms (D).

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Keywords
USPIO, MRI, SWI, Susceptibility, blooming effect, arteriogram, venogram, angiogram, MRAV.

No conflicts of interest to declare.

Assessment of an automated vein segmentation algorithm for MRI brain acquisitions at different field strengths

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Background: Several automated or semi-automated schemes have been proposed for intracranial vein segmentation (IVS) from MRI datasets. However, mainly due to the high variability of the susceptibility weighting of the contrasts at different strengths of the magnetic field (Bo), the assessment of IVS algorithms is usually performed at a fixed Bo value[1-3].

Objectives: To assess the performance of our fully automated multi-parametric IVS algorithm[4-5] (MAVERIC), originally intended and validated for 3 T MRI datasets, at different field strengths.

Methods: 3D double-echo spoiled gradient echo (GRE) sequences with flip angle close to the parenchyma Ernst angle were acquired at 1.5, 3 and 7 T in 4 volunteers. The voxel size and repetition- (TR) and echo- (TEs) times were chosen to provide similar susceptibility weightings at the different Bo in a clinically acceptable acquisition time:

- Bo=1.5 T: Resolution=0.7x0.7x1 mm^3; TR=36 ms; TE_{1-2}=[13.8;27.6] ms;
- Bo=3 T: Resolution=0.5x0.5x1 mm^3; TR=31 ms; TE_{1-2}=[7.38;22.14] ms;
- Bo=7 T: Resolution=0.5x0.5x0.5 mm^3; TR=25 ms; TE_{1-2}=[6.12;17.33] ms.

For each dataset, IVS maps were derived by the MAVERIC segmentation tool and 2 experienced neuroradiologists were asked to grade on a 0-5 scale (0 corresponding to the lowest reliability of the voxel classification; 5 reflecting an optimal compromise between sensitivity and specificity) the accuracy of 4 segmentation MIPped slabs (thickness of 20 mm) compared to the corresponding SWI mIPs.

Results: Illustrative segmentation results obtained at 1.5, 3 and 7 T are shown in Fig. 1, 2 and 3, respectively, where the obtained voxel classifications are placed side by side with the corresponding SWI and their fusion. The accuracy scores at 1.5, 3 and 7 T were 4.19±0.66; 4.44±0.51; 4.56±0.51, respectively. Scores obtained at 1.5 and 7 T were not significantly different from scores already assessed at 3T[4] (p=0.29 and p=0.50, respectively, at Mann-Whitney U-tests).

Conclusion: At all considered field strengths, MAVERIC provided comparably accurate IVS, given that visible vessel density increases with Bo.

Fig. 1. Segmentation result at 1.5 T. From left to right: MAVERIC-MIP; fusion of SWI-mIP with MAVERIC-MIP; SWI-mIP. Image projections cover 20 mm in the head-foot direction.

(Palma & Monti cont'd)

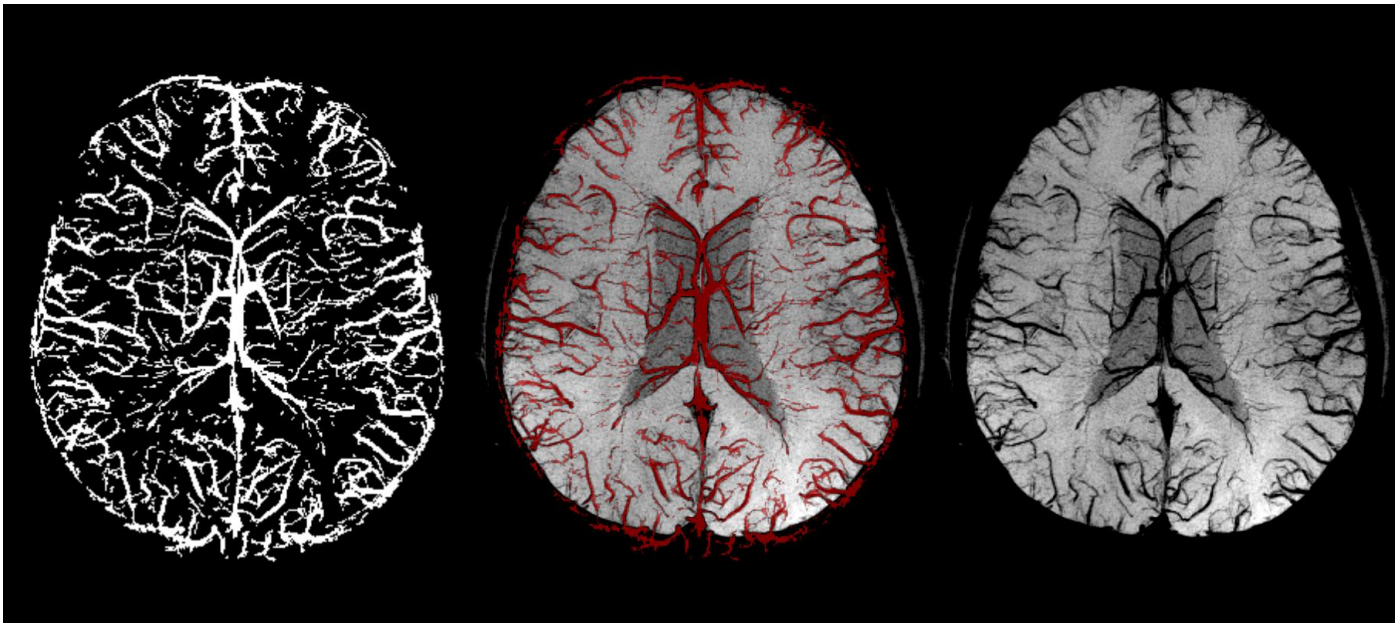

Fig. 2 Segmentation result at 3 T. From left to right: MAVERIC-MIP; fusion of SWI-mIP with MAVERIC-MIP; SWI-mIP. Image projections cover 20 mm in the head-foot direction.

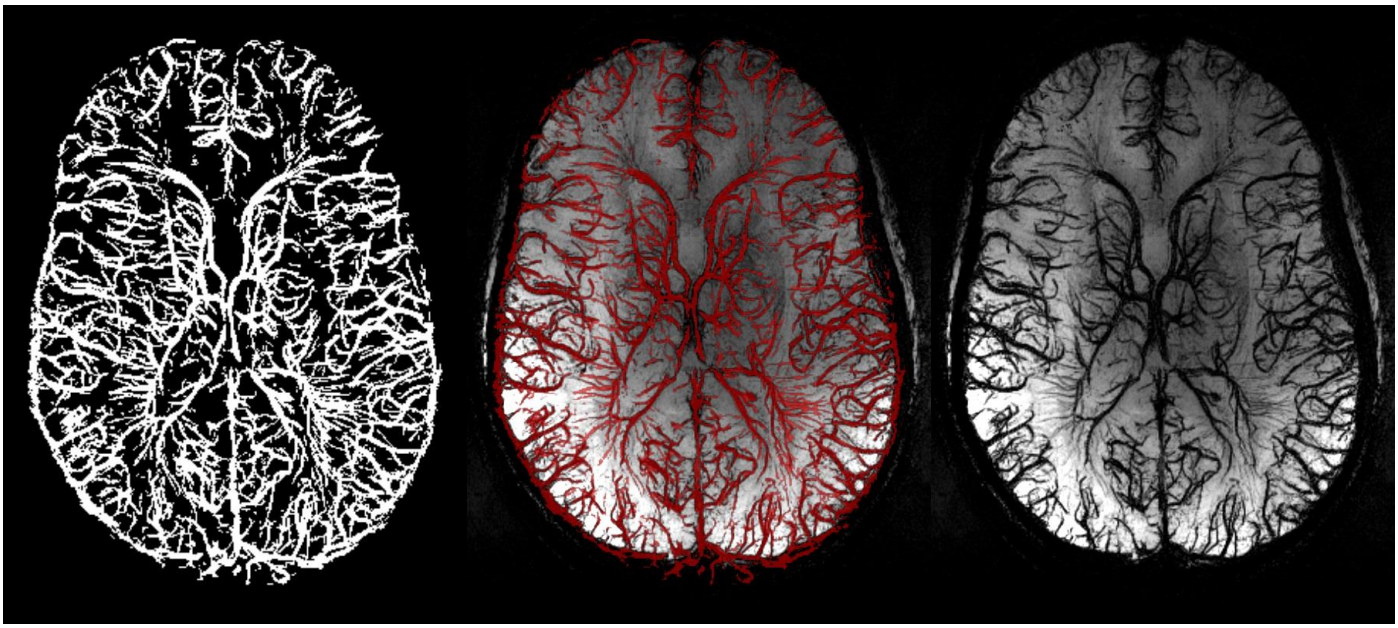

Fig. 3 Segmentation result at 7 T. From left to right: MAVERIC-MIP; fusion of SWI-mIP with MAVERIC-MIP; SWI-mIP. Image projections cover 20 mm in the head-foot direction.

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Keywords: brain veins, SWI, multi-parametric, segmentation.

The authors have nothing to disclose nor any conflict of interests in regards to this study.

Abnormal posture control of internal jugular vein flow is associated with brain atrophy progression in multiple sclerosis patients over 5 years

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Background: Chronic cerebrospinal venous insufficiency (CCSVI) has been associated with multiple sclerosis (MS). CCSVI is characterized by abnormalities of the main extracranial cerebrospinal venous outflow routes that interfere with normal venous drainage. No long-term studies examined evolution of brain pathology changes related to CCSVI, as assessed by MRI.

Objectives: To assess inflammatory and neurodegenerative brain changes in MS and age- and sex-matched healthy controls (HCs) over a period of 5 years.

Methods: This prospective study was performed in 87 MS patients and 36 HCs that were assessed at baseline and after 5 years using 3T MRI and venous hemodynamic (VH) extra-cranial and trans-cranial Doppler examinations. Both baseline and follow-up assessments were performed on the same equipment and by the same operators. Inflammatory MRI measures included analysis of T1 and T2 lesion volumes (LV) and new/enlarging lesions, while brain volume changes over the follow-up were used to assess neurodegenerative outcomes. Statistical analyses were performed comparing the evolution of brain pathology by CCSVI diagnosis (≥2 VH criteria) and each of the 5 VH criteria using non-parametric statistics.

Results: Abnormal posture control of internal jugular vein (IJV) flow [positive VH criteria 5 or negative Δ cross-sectional area (CSA)] showed the strongest association with brain volume changes in MS patients. MS patients with negative ΔCSA at baseline, had significant enlargement of ventricular cerebrospinal fluid (vCSF) volume (32.1% vs. 10.9%, p=0.001) and loss of whole brain volume (-3.9% vs. -1.9%, p=0.031) over 5 years compared to those without. MS patients with negative ΔCSA at follow-up, had significant loss of whole brain volume (-5.9% vs. -3%, p<0.001) and enlargement of vCSF volumes (23.8% vs. 10.4%, p=0.004) over 5 years compared to those without. There was a significant association of T1-LV accumulation over the follow-up and CCSVI diagnosis at baseline in MS patients (r=0.37, p=0.017). HCs with positive VH criteria 4 (no flow in IJV), positive VH criteria 5 and CCSVI diagnosis at baseline, showed a significant association with accumulation of new/enlarging T2 lesions (p<0.02) over the 5 years.

(Jakimovski, cont'd)

Conclusions: Abnormal posture control of IJVs is associated with development of global and central brain atrophy in MS patients over 5 years. CCSVI diagnosis is related to accelerated accumulation of T1 lesions in MS patients and T2 lesions in HCs over long-term.

Key words: multiple sclerosis, Doppler ultrasound, MRI, atrophy, lesions, healthy controls

Study disclosure:
This study was funded with internal resources of the Buffalo Neuroimaging Analysis Center. In addition, we received support from the Jacquemin Family Foundation.

Financial Relationships/Potential Conflicts of Interest:

Dejan Jakimovski, Karen Marr, Marcello Mancini, Sirin Ghandi, Maria Grazia Caprio, Deepa P. Ramasamay, Jesper Hagemeier, Niels Bergsland have nothing to disclose.

Bianca Weinstock- Guttman received honoraria as a speaker and as a consultant for Biogen Idec, Teva Pharmaceuticals, EMD Serono, Genzyme&Sanofi, Novartis and Acorda. Dr Weinstock-Guttman received research funds from Biogen Idec, Teva Pharmaceuticals,, EMD Serono, Genzyme&Sanofi, Novartis, Acorda.

Robert Zivadinov received personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health and Novartis for speaking and consultant fees. He received financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin-Coherus and IMS Health.

Automated Real-Time Quantitative Total Cerebral Blood Flow by Phase Contrast MRI

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Purpose

Cine phase contrast (PC) MRI is a well-established method to visualize and quantify pulsatile flow. However, pulsatile waveforms obtained using cine PC are an average cycle reconstructed using data acquired over multiple heartbeats. Therefore, this methodology is limited for real-time dynamic imaging and for determining physiologic beat-to-beat variations due to respiration or other manipulations. This work employed a recently developed real-time (RT) cine pc sequence to demonstrate the feasibility of automated real-time measurement of total cerebral blood flow (tCBF) by MRI. A pulsatility based segmentation (PUBS) was employed to overcome the challenge of lumen segmentation in the lower image quality and spatial resolution associated with RT PC. RT measurements of tCBF were compared with measurements obtained with conventional cine PC.

Materials and Methods

MRI data from two healthy subjects was obtained using 3T scanner (Skyra, Siemens Healthcare). Total CBF was obtained by summation of volumetric flow rate through the internal carotid and vertebral arteries. Automated segmentation of these lumens was achieved using the PUBS method which incorporates temporal information in each voxel to differentiate lumen pixels from background pixels (1). Real-time PC imaging was achieved with echo planar readout, parallel acceleration in the temporal direction, and shared velocity encoding (2). Imaging parameters include FOV of 172x196cm, acquisition matrix of 144x96, TR/TE of 129/9.6ms, VENC of 90cm/sec, and acceleration factor of 3. Conventional cine was acquired with higher temporal and spatial resolutions using TR/TE of 44/6ms and in-plane resolution of 0.5mm. Individual cardiac cycles were automatically identified by locating the onset of systole, which corresponds to the location of highest rate of increase in the flow rate. Total CBF and flow amplitude were then calculated for each heartbeat.

Results

Plots of the RT CBF waveform (blue) and the mean CBF in each heartbeat (red) are shown together with a representative cardiac cycle obtain using the conventional cine PC. The mean (SD) values of tCBF measure for this subject were 572 (47.7) mL/min vs. 646mL/min using the conventional cine. The mean (SD) value of the peak-to-peak flow amplitude obtained using the RT cine were 499 (51.5) mL/min, with a range of 368 to 602 mL/min vs. 559mL/mi with the conventional cine. Similar correspondence between the RT and the conventional cine measurements were found for the second subject. On average mean RT tCBF values were 11% lower than values obtained with conventional cine. Frequency analyses did not reveal respiratory modulation of tCBF.

Conclusion

The feasibility of automated dynamic measurements of total CBF by MRI has been demonstrated. While RT CBF measurements are slightly lower than flow rates obtained with conventional cine, likely due to lower resolutions, this small difference is well within normal fluctuations at rest. Dynamic quantitative RT imaging of CBF opens possibilities for new paradigms for interrogation of the cerebral hemodynamics.

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A Semi-automatic method for anatomical measures of the internal jugular veins

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Background and Objectives

The interest in measuring internal jugular veins (IJV) is growing due to the hypotized link between extra-cranial venous abnormalities and some neurological disorders[1]. Since IJV cross sectional area (CSA) values reported in the literature[2-4] disagree and are still not comparable, we proposed a semi-automatic method to measure and normalize the CSA and the degree of circularity (Circ) of IJVs along their whole length.

Methods

The IJVs of 36 healthy subjects (31.22 ± 9.29 years) were segmented on 2D time of flight magnetic resonance venography images acquired with a 1.5T Siemens scanner. IJV border was identified on a single axial slice, automatically propagated in 3D with Jim 6.0[5], and visually checked.
IJV CSA and Circ were automatically computed for slices between the first and the seventh cervical levels (C1-C7), and normalized among subjects by resampling, so that the C1-C7 height coincided with the mean group height.
Two-factor repeated measures ANOVA was performed to determine if the average CSA and Circ were significantly different among cervical levels (second factor: side). The inter- and intra-rater repeatability was assessed on 10 subjects with the intra-class correlation coefficient (ICC).

Results

IJV CSA and Circ were significantly different among cervical levels ($p<0.001$), without interaction with the side. A trend for side difference was observed for CSA (larger right IJV, $p=0.06$), but not for Circ ($p=0.5$). The highest CSA was found at C7 (right IJV: 79.98±42.39 mm^2), the lowest at C2 (left IJV: 37.47±19 mm^2); the highest Circ was observed at C3 level (right: 0.81±0.07) and the lowest at C1 (left: 0.73±0.1). Excellent agreements were obtained for all the measures (ICC>0.90).

Conclusion

This study proposed a reliable semi-automatic method able to detect the significant anatomical differences along C1-C7 and suitable for defining normality thresholds at each cervical level for future clinical studies.

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Keywords

Internal jugular veins, time of flight magnetic resonance venography, cross sectional area, degree of circularity.

None of the authors have anything to disclose nor any conflicts of interest in regards to this study.

Discovering the Complex Genetics of Idiopathic Normal Pressure Hydrocephalus

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Background. Idiopathic normal pressure hydrocephalus (iNPH) is a disorder of the aging brain in which unknown factors and comorbidities undermine the brain's elastant response to increased intracranial pressure (1). While current treatment is limited to surgery (2), a molecular/genetic understanding of iNPH will help identify presymptomatic people at risk and provide targets for drug therapy. As most cases of iNPH are sporadic, its genetics are assumed to be multifactorial, involving multiple genes of limited penetrance (effect). Recent results, however, have shown rare, highly penetrant (mendelian) genes in multifactorial disorders (3), a pattern seen in rare families in which iNPH segregates as a mendelian trait (4-10).

Objectives. This presentation will explain: 1. how the reverse genetic methods genome wide association, whole genome sequencing, and whole exome sequencing (WES; 11-13) can discover the candidate genes for iNPH; 2. how the protein-protein interaction networking method (14-16) can select the controlling proteins from those involved in the iNPH phenotype; 3. the complex genetics involved.

Methods. An example is given of a next generation sequencing (NGS; 17) approach, WES, in which variant (mutated) gene sequences are identified and annotated for the types of mutation and their functional impact. Cases and controls are compared for each variant to establish associations with phenotypes (11). This work is supplemented with a systems biology approach to create an "iNPH-ome." Similarity measures from public sources on the variants are used to blindly generate a protein-protein interaction network, whose properties show protein connectedness (lines in the illustration below), centrality of the protein in its connections (it's size), and to which family of functions it belongs (the clusters). Variant proteins with large centrality are candidates for drug therapy (14;15) and biomarkers for early disease detection.
Results and Conclusions. New genetic theory (18) and methods promise genomic solutions to previously intractable problems of complex inheritance, including those of iNPH. Problems arising from these methods, such as "missing heritability" and the clinical utility of the variants, are discussed.

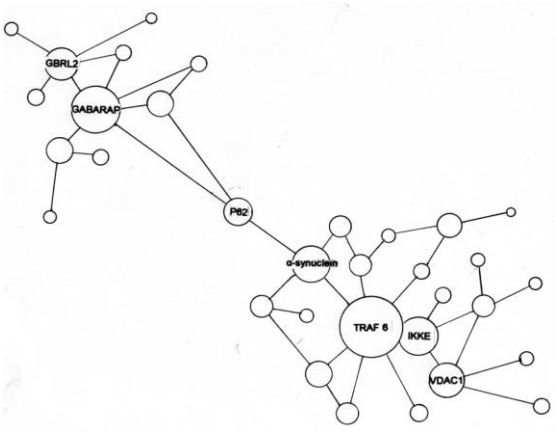

Illustration (hypothetical) of a protein-protein interaction network

(Prouty, cont'd)

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Dr. Prouty has nothing to disclose nor any conflicts of interest in regards to this study.

No association of extra-cranial venous abnormalities and clinical outcomes in multiple sclerosis patients over 5 years

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Background: Over the past decade, several studies attempted to investigate a causal association between abnormalities of extra-cranial venous system, known as chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS). There is limited literature regarding association of CCSVI with clinical outcomes in MS longitudinally.

Objectives: To assess the correlation between clinical outcomes in MS patients and extra-cranial venous abnormalities using Doppler examination over 5 years.

Methods: A longitudinal study was conducted at our center on 83 MS patients (47 relapsing-remitting (RRMS); 36 progressive (PMS) patients). Clinical assessment and venous hemodynamic (VH) extra-cranial and trans-cranial Doppler examinations were performed at baseline and follow-up with mean time period to follow-up being 5.5 years. The association of change in Expanded Disability Status Scale (ΔEDSS), confirmed disability progression (CDP) and relapse rate was investigated in MS patients with and without CCSVI diagnosis (≥2 positive VH criteria) and modified VH Insufficiency Severity Score (mVHISS) using VH criteria 3,4 and 5. Correlation analysis was corrected for age, gender and disease duration.

Results: Mean age of MS patients was 53.3 years (RRMS/ PMS=48.7/59.2 years) with median EDSS at baseline of 3.0 (RRMS/ PMS=2.0/5.3) and absolute change in EDSS of 0.5 (RRMS/ PMS=0.5/0.0). Relapse rate was 0.2/year in RRMS vs. 0.1/year in PMS and CDP occurred in 19 of 83 (22.9%) patients; RRMS vs. PMS=12 (25%) vs. 7 (19.4%). Mean mVHISS increase from baseline to follow-up was 1.2. CCSVI diagnosis at follow-up was present in 50 of 83 (60.3%) patients. In partial correlation analysis, no association was found between VHISS at baseline/ follow-up or mVHISS change and ΔEDSS or relapse rate. There was no significant association of CDP with CCSVI diagnosis at baseline/follow-up or mVHISS changes.

Conclusions: No associations of extra-cranial venous abnormalities and clinical outcomes of disease progression in MS patients over 5 years was detected.

Key words: multiple sclerosis, Doppler ultrasound, CCSVI, relapse rate, disability progression

Study disclosure:

(Gandhi, cont'd)

This study was funded with internal resources of the Buffalo Neuroimaging Analysis Center. In addition, we received support from the Jacquemin Family Foundation.

Financial Relationships/Potential Conflicts of Interest:

Sirin Gandhi, Marcello Mancini, Karen Marr, Maria Grazia Caprio, Dejan Jakimovski, Avinash Chandra and Jesper Hagemeier have nothing to disclose.

Bianca Weinstock- Guttman received honoraria as a speaker and as a consultant for Biogen Idec, Teva Pharmaceuticals, EMD Serono, Genzyme&Sanofi, Novartis and Acorda. Dr Weinstock-Guttman received research funds from Biogen Idec, Teva Pharmaceuticals,, EMD Serono, Genzyme&Sanofi, Novartis, Acorda.

Robert Zivadinov received personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health and Novartis for speaking and consultant fees. He received financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin-Coherus and IMS Health.

Endovascular treatment and stem cells therapy of CCSVI

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The goal of this study is to establish the clinical effect of the combined therapy – endovascular therapy of the chronic cerebrospinal venous insufficiency (CCSVI) and the regeneration therapy with stem cells in patients with MS (Multiple Sclerosis).

Methods: The research included 37 examined and treated patients with CCSVI: sick from MS. The neurological diagnoses were reached clinically with MRI. For the diagnosis of the vein obstruction – CCSVI were used Echo Doppler and phlebography. The autologic implantation of stem cells was taken from bone marrow, and after the cleaning of the cells, the same day was done the implementation in the carotid and vertebral arteries. Simultaneously with the implantation was done and endovascular therapy with CCSVI-dilation, or stenting of the jugular veins.

Results: Endovascular therapy was conducted on the sick patients with both various neurodegenerative diseases and diagnosis of CCSVI: venous dilation and/or stenting of the venous stenosis of jugular vein, brachiocephalic vein and azygos vein. Postprocedurally angiographic result was positive. In every case in addition was carried out an autologic implantation of stem cells from bone marrow. The combined therapy reported clinical effects: 67% of the patients had positive clinical effects, 70 % had increase in QOL in patients suffering from MS, EDSS dropped from 5.6 before to 5.1 after the procedure. The patients had improvements in motor function, coordination, sensitivity, visual and cognitive function. The early or late restenosis accounted for 29%. Clinical decline was observed in only 8 % of the cases.
Conclusion: The improved vein drainage after endovascular therapy of CCSVI, combined with regeneration therapy with stem cell from bone marrow had very good clinical effect with low number of post-procedure complications.

Keywords: CCSVI, stem cells, MS.

None of the authors have anything to disclose nor any conflicts of interest in regards to this study.

CCSVI PREVALENCE IN MENIERE'DISEASE AND PRELIMINARY RESULTS OF BALLON VENOUS ANGIOPLASTY

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Purpose: To evaluate by means of Doppler ultrasound, MRI and phlebography, the relationship between Meniere's Disease and chronic cerebrospinal venous insufficiency (CCSVI) and to test whether angioplasty is an effective procedure in improving symptoms.

Materials and Methods: 1) Phase 1: 182 patients diagnosed with definite Meniere's Disease (AAO 1995 and AAO 2015) who had gained no benefit from medical therapy, underwent echo-enhanced color Doppler sonography using-Zamboni's protocol to check for CCSVI. 102 healthy subjects matched by age and gender acted as controls. 2) Phase 2. 135 Positive for CCSVI underwent MRI of the Brain and of the Neck. 3) Phase 3. In 70 positive subjects we performed a venogram and the diagnosis of associated CCSVI was confirmed. These patients were treated by angioplasty of the Internal Jugular Vein, then re-tested according to the baseline scales of Meniere's diseases. Twenty-two of them had a 24-month follow.up.

Results: Out of a total of 182 patients with Meniere's disease, an ultrasound and MRI diagnosis of CCSVI was made in 162 patients (89%). Only 12% of healthy showed signs of CCSVI. In forty patients venography confirmed the CCSVI diagnosis and PTA proved to be effective in 80% of patients, with significant improvement of several scales of audiological and vestibular function at 24 month follow-up. The results were, independently, assessed by three ENT center.

Conclusions: The prevalence of CCSVI in patients with Meniere's Disease is higher than in healthy subjects. Audiological and vestibular functions seemed to improve with PTA in the majority of patients.

Abbreviations: MD: Meniere Disease; MS: Multiple Sclerosis; CCSVI: Chronic cerebrospinal venous insufficiency; PTA: Percutaneous transluminal angioplasty; IJV: Internal jugular vein.

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Conflict of Interest: None.

Multiple Sclerosis and Symptom Changes after PTA: 4 year regular follow up on 366 Patients

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Multiple Sclerosis is perhaps the globally mostly highlighted neurological degenerative disease of the recent years and venous abnormalities are always more observed (1). The numbers of papers written on chronic cerebrospinal venous insufficiency (CCSVI) are now countless but, still, the official neurologic therapy and research appears to ignore these abnormalities regarding the Extracranial Venous System. Still actually the aim is set upon drugs (2,3,4) that have their goal on the plaque activity that is constantly and always better monitored through MRI (5,6), but very little is oriented upon patients' symptoms and vein-flow hemodynamics.

A recent publication (7), based on a follow-up of a significant number of MS patients with a positive CCSVI diagnosis that underwent to venous percutaneous transluminal angioplasty (PTA), demonstrates that symptoms may improve. Moreover symptom improvements are parallel with a better venous outflow while they worsen in vein re-stenosis situations.

The work regards 366 patients that regularly underwent to Duplex exams before and after vein angioplasty, divided into the three most frequent neurologic severity classifications: Relapse-Remitting; Secondary-Progressive and Primary-Progressive and expanded disability status scale- EDDS (8) score. All patients were interviewed prior to Duplex exams with the intent to collect and classify their most frequent symptoms and to monitor eventual changes. The follow-up was collected for 48 months. A data base revealed eleven most frequent disturbs and symptoms, together with working capacities, and was kept up-to date at every Duplex control aiming to establish a novel rapid CCSVI symptoms questionnaire assessment in 4 years follow up.

The most frequently described symptoms were: diplopia, fatigue, headache, upper limb numbness/mobility, lower limb numbness/mobility, thermic sensibility, bladder control, balance coordination, quality of sleep, vertigo, mind concentration.
The patients, gender and disease severity that matched with this symptom classification were: 264 (72%) Relapse-Remitting (RR): 179 females (67.8%) and 85 males (32.2%); 62 (17%) Secondary Progressive (SP): 37 females (59.7%) and 25 males (40.3%); 40 (11%) Primary Progressive: 22 females (55%) and 18 males (45%).

Results appear to be significantly good in the RR group, also the biggest one. Diplopia improved in 262/264 patients (99.2%) ($P<0.0001$); fatigue in 260/264 (98.5%) ($P<0.0001$); headache in 205/208 (98.6%) ($P<0.0001$); balance coordination in 23/26 (88.5%) ($P<0.0001$); quality of sleep in 55/59 (93.2%) ($P<0.0001$); vertigo in 30/33 (90.9%) ($P<0.0001$); mind concentration in 142/144 (98.6%) ($P<0.0001$). Other results regarded: upper limb numbness and mobility in 20/24 (83.3%) ($P=0.0002$); lower limb numbness and mobility 13/15 (86.7%) ($P=0.0087$); thermic sensibility 3/4 (75%) [P: not significant (n.s.)]; bladder control 2/3 (66.6%) (P: n.s.).

In contrast in the Progressive cases results appeared quite different where, nevertheless, some useful considerations were collected and statistically significant, too. In addition, venous angioplasty in this series resulted to be safe since side effects were observed only in seven patients (0.19%) that grew a

(Bavera, cont'd)

monolateral jugular thrombosis but still were regularly controlled and above all did not suffer worsening of the disease.

Therefore PTA results, above all in the RR group, bring to say that the correct criteria should be "the sooner the better", with general symptom and life quality improvements. Nevertheless, fewer but still useful improvements are present also in the Progressive groups of patients.

Moreover, this could introduce to a "new concept" in classifying the disease that in most cases isn't clinically always the same and doesn't develop the same way. The actual severity scale therefore isn't just the one based uniquely on the number or location of lesions, active or not, or upon the EDSS mobility scale, but upon a Patient's Symptom Scale that also represents the dignity and lifestyle of the single individual.

Now that CCSVI is a worldwide-demonstrated pathology (9,10), the direction is towards improvements in technology and materials to evaluate and maintain a correct venous outflow.

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Keywords: Multiple Sclerosis; CCSVI; Venous Angioplasty; Neurologic Symptoms.

Dr. Bavera has nothing to disclose nor any conflicts of interests in regards to this study.

A first step towards a mathematical model for the human lymphatic system

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Background: Louveau et al. [1] and Aspelund et al. [2] have recently discovered the existence of meningeal (dural) lymphatics in the Central Nervous System (CNS). The lymphatic network is a one-way transport system connected to other fluids, such as cerebrospinal fluid, interstitial fluid and blood flow. The lymphatic system is responsible for the clearance of excess fluid, proteins and waste products, as well as for transport of immune cells. It would be of interest to understand the complex interaction of these fluid systems from a bio-physical point of view.

Objectives: To design a mathematical model for the complete extra-cranial lymphatic system, with a view to extend the model in the future to include the newly discovered CNS lymphatic system.

Methods: Using our developed mathematical model, we perform simulations to compute flow and pressure field in a network of lymphatic vessels.

Results: Here we first show numerical results of the experiments proposed by Davis et al. [3] for a single lymphangion containing two valves. The mathematical model is able to reproduce the rhythmic, spontaneous lymphatic contraction that generates the pressure needed to open the downstream valve, see Fig. 1. Results for a more complex network of vessels will be shown at this conference.

Conclusions: Our preliminary results suggest that the construction of a mathematical model for the complete lymphatic system, including the CNS, is feasible. This would open the possibility to perform simulations of the dynamics of all fluid systems involved, in a holistic approach, by making use of the recently developed Müller-Toro [4] mathematical model for the circulation.

Keywords: Mathematical modelling - Collecting lymphatics - Meningeal lymphatics - Human lymphatics circulation

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(Contarino, cont'd)

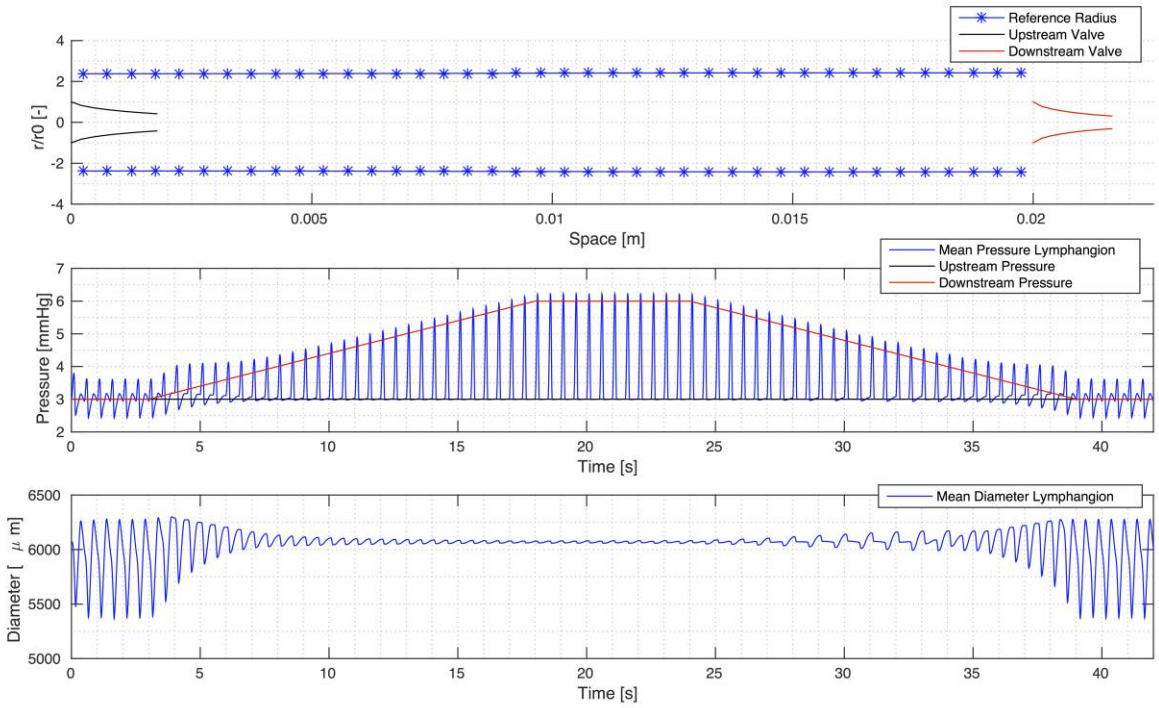

Figure 1: Numerical simulation of a lymphangion. Top frame: Illustration of a lymphangion configuration at a fixed time with upstream (left) and downstream (right) valves. Middle frame: Mean pressure against time. Bottom frame: Mean diameter against time.

Dr. Contarino has nothing to disclose nor any conflicts of interests to report in regards to this study.

Upregulation of lymphatic markers and vascular adhesion molecules in CNS RNAseq transcriptome of a viral model for multiple sclerosis

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). MS has also been proposed to be a vascular disease, since the expression levels of lymphatic markers and vascular adhesion molecules have been extensively demonstrated in association with disease activity. Although the precise cause(s) of MS is/are unknown, viral infections have been associated with MS. Theiler's murine encephalomyelitis virus (TMEV) is a non-enveloped, positive-sense, single-stranded RNA virus that can cause TMEV-induced inflammatory demyelinating disease (TMEV-IDD) with viral persistence in the spinal cord of mice. TMEV-IDD has been used as a viral model of MS. We aimed to clarify the involvement of lymphatic and blood vessels, using the RNA sequencing (RNAseq) transcriptome data of mice infected with TMEV. We found upregulation of several lymphatic markers, including podoplanin (1.4-fold, $P < 0.05$) and angiopoietins (1.2-fold, $P < 0.01$), and vascular adhesion molecules, particularly ICAM-1 (4.5-fold, $P < 0.01$) and VCAM-1 (1.8-fold, $P < 0.01$), as well as their ligands on T cells, LFA-1 (37.2-fold, $P < 0.01$) and VLA-4 (2.5-fold, $P < 0.01$), respectively, in the spinal cord, but not in the spleen. Principal component analysis (PCA) using the RNAseq data of these molecules showed that LFA-1/ICAM-1, VLA-4/VCAM-1, and other adhesion molecules contributed to separation between control and TMEV-infected samples. Thus, these molecules may play a key role in TMEV-IDD.

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Omura S et al., Bioinformatics multivariate analysis determined a set of phase-specific biomarker candidates in a novel mouse model for viral myocarditis. *Circ Cardiovasc Genet*. 2014, 7:444-454.

Keywords: Animal Model, Bioinformatics, CNS Demyelinating Disease, Blood-Brain Barrier, Vascular Diseases

None of the authors have anything to disclose or conflicts of interests in regards to this study.

Traumatic Brain Injury (TBI) Severity Quantification and Outcome Prediction Using MRI

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Background: TBI affects almost 2.5 million people annually in the United States alone, causing almost 53,000 deaths annually (CDC, 2010). MRI techniques have proven to be effective in assessing both hemorrhagic and diffuse axonal damage resulting from TBI.

Objectives: To use Susceptibility Weighted Imaging (SWI) and T2 Fluid-Attenuated Inversion Recovery (FLAIR) to quantitatively classify TBI damage in order to predict clinical outcome.

Methods: A group of 20 TBI patients were imaged on a 3T Siemens scanner at Epworth Hospital in Clayton, Australia. Susceptibility Weighted Imaging Maps (SWIM) were produced using SPIN software (MR Innovations, Inc., Detroit, MI). SWI images were assessed for Cerebral Microbleeds (CMBs), macrobleeds, and venous damage. Using SWIM, CMBs were determined by setting a threshold of 50 parts per billion as well as ensuring their visibility in SWI and phase images. They were then categorized by location, size, and susceptibility. FLAIR images were assessed for Diffusive Axonal Injury (DAI). All four types of damage were weighted using the following scale: Based on the work of Wu3, the brainstem received the highest damage score, followed by the corpus callosum and peduncle, followed by the remainder of the brain. In addition,scores were weighted based on damage type. The cumulative scores were then calculated for each case and plotted against the Post Traumatic Amnesia (PTA) and Glasgow Coma Score (GCS) scores.

Results: Of the 20 cases, 12 showed two or less CMBs, 11 showed no macrobleeds, 6 showed no venous damage, and 5 showed no DAI. Patient PTA ranged from 0.5 to 63 days and GCS scores from 3 to 15. When the scores from all four types of damage are summed and plotted, a linear trend appears.

Conclusion: TBI severity as determined by CMB weighted findings appears to correlate with outcome.

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Keywords: TBI, FLAIR, SWI, and SWIM

None of the authors have anything to disclose or any conflicts of interests in regards to this study.

6 SUBMITTED ABSTRACTS – POSTER

HIGH RESOLUTION M-MODE CHARACTERIZATION OF JUGULAR VEINS VALVES IN HEALTY VOLUNTEERS AND IN PATIENTS WITH NEUROLOGICAL DISORDERS

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Objective:

Recently a high prevalence of valve absence was found in the internal jugular vein (IJV) of healthy volunteers by means of M-mode high resolution sonography.[1] Surprisingly, it has been demonstrate a valve absence just on one side in 46% and bilaterally in 16% of cases; however it still has not been known the prevalence of valve absence in neurological and/or neurosensory disorders.[1]

Non-invasive and invasive high resolution sonography reported high rate of intraluminal obstacles and defective valves in chronic cerebrospinal venous insufficiency (CCSVI), a condition found associated to several neurological and/or neurosensory disorders.[2-8]

Aim of the present study is to compare the IJV valve presence or absence by means of M-mode, together with morphology and motility of the leaflets in patients and in healthy controls (HC).

Methods:

A cohort of 253 subjects underwent to high resolution echo colour Doppler (ECD) investigation of the neck veins, including M-mode evaluation of the IJVs junction valve plane, in standardized postural and respiratory conditions. Primary outcome measure was characterization of valve presence, morphology and motility. Secondary outcome was CCSVI ECD screening. The cohort was subdivided into: 83 healthy volunteers (35M - 48F, 25.7±6.7 y.o.), 71 multiple sclerosis (MS) (35M-46F, 40±10 y.o.), 79 sudden sensorineural hearing loss (SSNHL) and 20 Meniere disease (43M - 56F 59±12.8 y.o).

Results:

Primary outcome: Bilateral valve presence was found in 32 subjects out of 83 (38%) HC, 41 subjects out of 71 (58%) MS (p<0.0233), 23 subjects out of 79 (29%) SSNHL (p=NS), 2 subjects out of 20 (10%) Meniere disease (p<0.0166).

Moreover, bilateral valve absence was recorded in 13 out of 83 (16%) of HC, 7 out of 71 (10%) MS (p=NS), 23 out of 79 (29%) SSNHL (p<0.0578), 8 out of 20 (40%) Meniere disease (p<0.0272).

Finally, monolateral valve presence occurred in 38 out of 83 (46%) HC, 23 out of 71 (32%) MS (p=NS), 33 out of 79 (42%) SSNHL (p=NS), 10 out of 20 (50%), Meniere disease (p=NS).

The prevalence of bicuspid morphology was found out in 57 out of 102 IJV valves (56%) of HC, 26 out of 105 (25%) MS (p<0.0001), 13 out of 79 (16%) SSNHL (p<0.0001), 4 out of 14 (29%) Meniere disease (p:n.s.). To the contrary, monocusp morphology was found in 45 out of 102 (44%) in HC, 79 out of 105 (75%) MS (p<0.0001), 66 out of 79 (84%) SSNHL (p<0.0001), 10 out of 14 (71%) Meniere disease (p:n.s.).

Interestingly, the valve leaflets were found mobile in all HC cohort whereas fixed valve leaflets were recorded in 86 out of 105 (82%) MS (p<0.0001), 32 out of 79 (41%) SSNHL (p<0.0001), 6 out of 14 (42 %) Meniere disease (p<0.0001).

Secondary outcome: None of healthy volunteers were positive for CCSVI while 65 out of 71 (92%) MS ($p<0.0001$), 66 out of 79 (83%) SSNHL ($p<0.0001$), 16 of 20 (80%) Meniere disease ($p<0.0001$), were positive for CCSVI screening.

Conclusions:
The development of the jugular valve was found out significantly different in MS category respect to HC and in turn to other patients, the latter showed a higher rate of bilateral absence and monocusp morphology.
Moreover, regarding valve motility all patients category showed a higher rate of not mobile leaflets respect to HC, this finding finally determine a higher prevalence of CCSVI ultrasonographic criteria among all patients groups.
A further analysis will be desirable in order to objectively quantify the venous outflow through the main pathways or through the collateral routes standardized with the individual arterial in-flow.
No Conflict of Interest Declared.

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Key Words: Cerebral Venous Drainage, Duplex Ultrasound, M-Mode, Internal Jugular Vein Valves, Chronic Cerebrospinal Venous Insufficiency.

None of the authors have anything to disclose nor conflicts of interests in regards to this study.

Multi-parametric algorithm for the automated segmentation of brain vein

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Background: Cerebral vein analysis provides a fundamental tool to study neurovascular diseases. The assessment of vascular anatomy from a MR scan by means of manual segmentation of the cerebral veins is daunting and observer-dependent; therefore, automated approaches are actively sought for[1-3], as they also improve reproducibility.

Objectives: to present an algorithm for Multi-parametric Automated Vein Reconstruction (MAVERIC) that implements at once structural, morphological and relaxometric criteria of vein characterization to enhance classification accuracy.

Methods: A 3D double-echo spoiled gradient echo (TR=31ms, TE_{1-2}=[7.38;22.14] ms, resolution=0.5x0.5x1mm^3, flip angle=13°) sequence was acquired once on 4 healthy controls, and twice on another subject, with head repositioning between the scans.
For each dataset SWI images (structural content), Vesselness (morphological information) and R2* (relaxometry) maps were derived. Based on the assumption that vein voxels have low SWI intensity, high Vesselness and R2* values, MAVERIC iteratively refines a vein mask by adding newly detected vessel voxels that satisfy the following criteria:

- SWI<mean(SWI)–2.5*std_dev(SWI)
- Vesselness>mean(Vesselness)+std_dev(Vesselness)
- R2*>mean(R2*)

Where the statistical moments were locally computed on a spherical moving window, excluding previously marked voxels. The exit condition for the iteration is verified when less than 1‰ of the voxels are added.

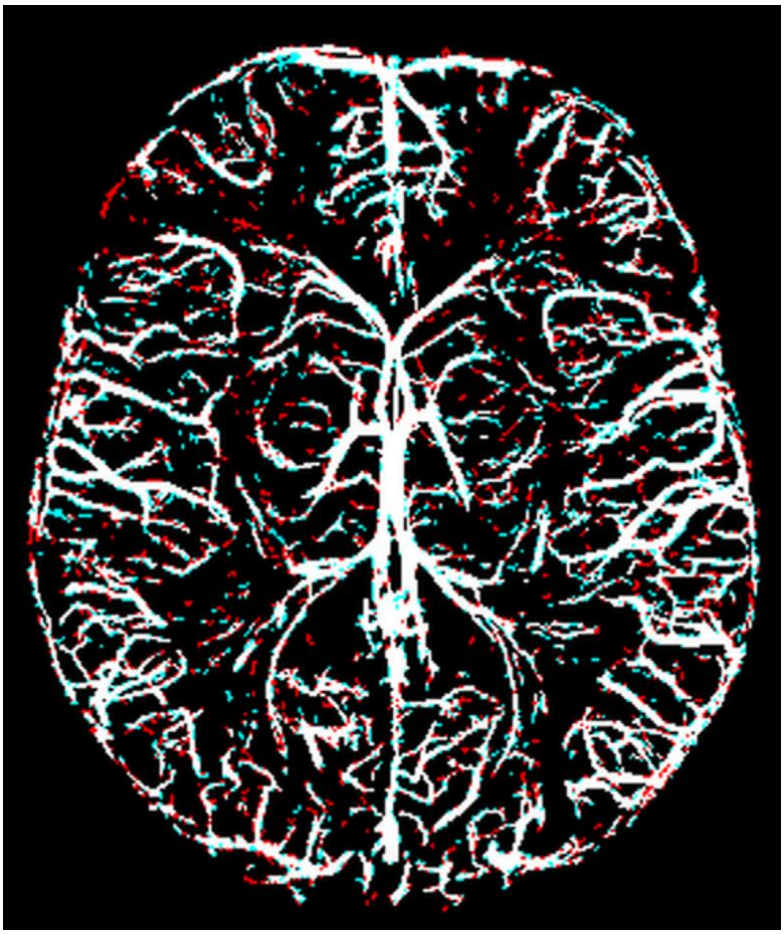
For each dataset, the performance of MAVERIC was compared to previous mono/bi-parametric[1,4] (m/bPS) approaches by blindly grading on a 0-5 scale the accuracy of vascular tree depiction on 4 MIPped slabs (thickness: 20 mm). To assess inter-scan reproducibility, the difference between pre- and post-repositioning segmentations (S_{pre} and S_{post}) were expressed as Modified Hausdorff Distance[5] (MHD) of the co-registered vein masks.

Results: m/bPS maps were never preferred to the corresponding MAVERIC maps in the test-sample. The mean accuracy scores were 4.44±0.51 for MAVERIC vs 3.38±0.62 for m/bPS. Comparison of S_{pre} and S_{post} showed a good overlap with a MHD of 0.33mm.

Conclusion: Combining information from SWI, Vesselness and R2* maps led to a reduction of false positives coupled to an improved detection of true positives, outperforming the m/bPS. The algorithm exhibits excellent inter-scan reproducibility, with a MHD that was well below the resolution of the used dataset.

(Monti and Palma, cont'd)

Fig. 1 RGB color coded fusion of S_{pre} (red) and S_{post} (cyan) maps, MIPped over 20 mm in the head-foot direction. White areas correspond to matched vein detections.



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Keywords: brain veins, R2* map, SWI, Vesselness, multi-parametric segmentation, reproducibility.

None of the authors have anything to disclose or any conflicts of interests in regards to this study.

Centralized and local Doppler sonography reading agreement for diagnosis of the chronic cerebrospinal venous insufficiency (CCSVI)

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Background: Chronic cerebrospinal venous insufficiency (CCSVI) is characterized by abnormalities of the main extracranial cerebrospinal venous outflow routes, which can be detected by Doppler sonography (DS) using 5 venous hemodynamic (VH) criteria. A cutoff for CCSVI diagnosis classification consists of ≥2 abnormal DS VH criteria. Given that multiple VH criteria are acquired, the reproducibility of the categorical CCSVI diagnosis depends on the blinding, training level, skills of the operator and interpretation of the VH criteria.

Objectives: To assess agreement between centralized and local reading of DS examination for diagnosis of CCSVI in trained Doppler sonologists.

Methods: This study was performed in 87 multiple sclerosis (MS) patients and 36 age- and sex-matched healthy controls (HCs) who obtained DS examination by a single CCSVI-trained expert sonologist blinded to the subject disease status. All study subjects were positioned and draped (covered with a blanket, leaving only the head and neck exposed) on the DS chair by the unblinded study coordinator. The VH DS criteria included: (1) reflux present in an outflow pathway [internal jugular vein (IJV) and/or vertebral vein (VV)] with the head at 0° and 90°; (2) reflux in the intracranial veins/deep cerebral veins; (3) high resolution B-mode evidence of proximal IJV narrowing and/or other B-mode anomalies; (4) flow not detectable in the IJVs and/or VVs despite numerous deep inspirations; and (5) abnormal posture control of IJV flow. After the local Doppler sonologist performed the investigation, all images and video clips of the DS examination were sent to the centralized reading center, where a second blinded reading was performed by two CCSVI-trained expert sonologists. Statistical analyses were performed comparing accuracy of CCSVI diagnosis (≥2 VH criteria) and each of the 5 individual VH criteria using Cohen kappa statistic, along with positive/negative agreement and Odds ratio (OR) with 95% confidence intervals (95% CI).

Results: Diagnosis of CCSVI was obtained in 59.7% of local and 64.3% centralized readers (Kappa, 0.67, p<0.001). The highest Kappa between local and centralized readers was observed for VH criteria 2 (0.93) followed by VH criteria 5 (0.70), VH criteria 1 (0.66), VH criteria 3 (0.64) and VH criteria 4 (0.58). Similar Kappa values were obtained for CCSVI diagnosis and individual CCSVI criteria in MS patients and HCs. The positive predictive value (PPV) and negative predictive value (NPV) for CCSVI diagnosis was 82.7% and 86,7%, respectively with an OR of 31.1 (95% CI 11.1-87.5, p<0.001). The highest agreement between local and centralized readers was observed for VH criteria 5 (OR 98.7, 95%CI 17.1-569.9, p<0.001) with 72.7% PPV and 97.3% NPV followed by VH criteria 2 (OR 53, 95% CI 13.4-209.2, p<0.001) with 98.1% PPV and 100% NPV value.

Conclusions: Centralized reading of the DS examination for the diagnosis of CCSVI is feasible with high accuracy in CCSVI-trained Doppler sonologists. The most reproducible VH criteria between local and centralized readers were VH criteria 5 and 2.

Key words: Doppler sonography, reader agreement, multiple sclerosis, healthy controls, venous hemodynamic criteria

Study disclosure:
This study was funded with internal resources of the Buffalo Neuroimaging Analysis Center. In addition, we received support from the Jacquemin Family Foundation.

Financial Relationships/Potential Conflicts of Interest:

Marcello Mancini, Karen Marr, Maria Grazia Caprio, Jesper Hagemeier, Sirin Ghandi, Dejan Jakimovski and Avinash Chandra have nothing to disclose.

Bianca Weinstock- Guttman received honoraria as a speaker and as a consultant for Biogen Idec, Teva Pharmaceuticals, EMD Serono, Genzyme&Sanofi, Novartis and Acorda. Dr Weinstock-Guttman received research funds from Biogen Idec, Teva Pharmaceuticals,, EMD Serono, Genzyme&Sanofi, Novartis, Acorda.

Robert Zivadinov received personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health and Novartis for speaking and consultant fees. He received financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin-Coherus and IMS Health.

Venous flow abnormalities associated with Parkinson's disease using MRI: Pilot Study

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Objective: To assess internal jugular vein (IJV) structure and blood flow in patients with Idiopathic Parkinson's disease (IPD).

Background: The cause of IPD is unknown. Previous research has shown a potential link between alterations in neurovascular status and IPD. Chronically obstructed extra-cranial drainage pathways such as the IJVs could cause increased resistance within the cerebral venous system in IPD patients.

Methods: A Siemens 3T MRI system was used to assess the head and neck venous vasculature of 18 IPD patients. Stenosis was determined using 2D-TOF MRV and 3D TRICKS venography and using thresholds consistent with other literature[a]. Venous flow at the C6/C7 vertebral level was measured using a Phase Contrast (PC) MRI sequence. Flow rate ratios between the dominant and sub-dominant side IJVs were made. All quantitative analysis was performed using SPIN Software (Detroit, MI, USA).

Results: Pilot study results indicate that 11 of 18 (61%) IPD cases demonstrated some anomaly (stenosis, compression or lack of signal) in either the transverse sinus or internal jugular vein using MR venography. Summed IJV flow (right IJV + left IJV) at the C6/C7 vertebral level was greater than 8 ml/sec and consistent with a cohort of healthy controls that had been previously assessed[b]. However, flow measurements show 4 of 18 (22%) cases present with a dominant to subdominant flow ratio of greater than 4 to 1 which is not consistent with the previously assessed healthy controls[b]. Seven of the 18 cases (39%) show dominant:subdominant transverse sinus flow ratios > 5:1 with six of them showing right dominance. The preponderance of cases with this trait is consistent with a previous study of IPD patients from Wuhan Hospital in China[c].

Conclusions: This initial study serves to examine the potential of venous flow abnormalities occurring in IPD patients, however further investigation is needed to confirm these preliminary statistics.

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None of the authors have anything to disclose or any conflicts of interests in regards to this study.

Speculation that CCSVI and related MS is Caused by prlonged undetected Vasospasm of the OJV and Azygos Vein

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Synopsis:
Multiple Sclerosis is a disease characterized by demyelination of axons as well as chronic inflammation. Multiple sclerosis exists in several forms; the majority of patients demonstrate relapsing and remitting mode of disease. However, yet no findings or speculation made about the etiology of relapse and remit. In early phase, multiple sclerosis often associated with autonomous dysregulation such as thermoregulatory dysbalance "hot and cold, chills and diaphoresis, bizarre dreams, tachycardia, and migraine headaches. In progressive form, it may present itself with dysesthesia of the upper and then lower extremities. Speculation of initial cause of inflammation, encephalomyelitis, is still controversial. The main dogma" If not viral agent, then autoimmune process!" still Influence etiologic view.
It is speculated that "CCSVI" and related multiple sclerosis caused by prolonged, undetected vasospasm of the Internal Jugular vein, and azygos vein. Intensive studies since 2009 reported by Zamboni et all revealed retrograde back flow of venous content is particularly relevant for the neurodegenerative status in CCSVI, and related multiple sclerosis, which presents its damage at different brain level.

Purpose:
Based on the hypothesis of autonomous nerve switch setting toward autonomic nervous system dysregulation by disproportional sympathetic activation or parasympathetic withdrawal, we out sourced 5 patients with different behavior of multiple sclerosis.

Method:
Patients were randomly selected at our clinic. Informed consent obtained. A sterile mixture of medication dexamethasone/lidocaine/thiamine prepared and administered directly into the peri – venous space of internal jugular veins.

Results By
continuous follow-ups and ultrasound diagnostic imaging at 1, 2, 3, 4, 12, and 48 weeks, status of IJV evaluated for continuous flow and vasodilation. We found extremely satisfactory results associated with neurological improvement in these five patients.

Conclusion:
Alternative administration of dexamethasone/lidocaine/thiamine mix perivascularly allows appropriate penetration of adventia and muscularis layer of the vein. It is tolerable and less aggressive.

Conflict of interest and Disclosure: Author has no financial relationship with any organization. The study was sponsored by Corona doctor's medical clinics in Corona, CA.

Rare case of Bi-frontal ischemic Stroke Resulting from low voltaje electrical injury with pre-existing Anatomic Various in Circle of Willis

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Shreveport, LA

OBJECTIVE: To report a rare case of bi-frontal ischemic stroke resulting from low voltage electrical injury with pre existing anatomic variations in Circle of Willis (CW).

BACKGROUND: Stroke is a rare and serious complication of electrocution. There are few case reports concerning watershed strokes due to cardiac arrhythmia after lightening injury. Intra cranial vasospasm and resulting ischemic stroke due to low voltage electrical shock has been rarely reported. We will discuss that pre existing anatomic variations in CW can complicate the clinical course further.
METHOD: Case report/chart review

RESULTS: A 39 years old male was found confused with a piece of electric wire in his hand with a second degree burn. CT scan brain showed multiple ischemic strokes. Neurological examination revealed Wernicke's aphasia with "word salad" speech, poor comprehension and repetition. Motor examination showed weakness 4/5 in right arm, symmetrical reflexes and mute plantar responses. Sensory and coordination assessments were limited due to agitation. Stance and gait examination revealed wide based stance with an ataxic gait. Urine drug screen showed no substances and serum myoglobin was elevated. Echocardiogram and carotid ultrasound were unremarkable and continuous cardiac monitoring showed no arrhythmia. MRI brain showed acute ischemic stroke in both frontal and left basal ganglia region. Brain MRAngiography revealed bi-hemispheric left anterior cerebral artery and narrowing/vasospasm of left Middle cerebral artery. No further intervention was done. He was started on aspirin and his further clinical course remained stable. He was discharged to a rehab facility. Our patient is the only in literature presenting with ischemic strokes due to low voltage electric injury stemming from anatomical variations in CW along with transient vasospasm and possible cardiac arrhythmia as the likely mechanisms.

CONCLUSION: Low voltage electric shock can lead to multiple ischemic strokes by various mechanisms in anatomically predisposed patients, requiring early clinical intervention.

Key words: Electrical Injury, Ischemic Stroke, Bifrontal ACA (anterior cerebral artery)
References:

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   Yeh Huan-Jui, Liu Chih-Yang,[1] Lo Huei-Yu, and Chen Po-Chih
2. Neurological complication after low-voltage electric injury: a case report
   Kim HM[1], Ko YA[2], Kim JS[1], Lim SH[1], Hong BY[1]

None of the authors have anything to disclose or any conflicts of interests in regards to this study.

Comprehensive cerebral flows analyses of MRI acquired data following a chiropractic intervention of migraine subjects

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Objectives:
The objective of these analyses quantified CSF and cerebral blood flow of eleven migraine subjects while evaluating venous anatomy for structural anomalies. Recent research has shown a link between insufficient venous blood flow and migraine (1). Cerebral flow data collection occurred, before and after an intervention that utilized the atlas correction procedure of the National Upper Cervical Chiropractic Association (NUCCA).

Methods:
Eleven neurologist diagnosed migraine headache subjects were scanned at baseline, four and eight-weeks after the intervention. Following an institutional review board approved study protocol; data were collected at one imaging site, using a 1.5 Tesla GE Optima scanner (GE Medical Systems, Waukesha, WI). Two blinded examiners analyzed acquired data using Signal Processing in nMRI (SPIN) software (MR Innovations, Detroit, MI).

Flow analyses used conventional MR brain imaging, two-dimension time-of-flight magnetic resonance venography data for anatomical assessment, and phase contrast flow quantification of cerebrospinal fluid (CSF) and venous flows. A paired t-test (Microsoft Excel, Redmond, WA) compared venous outflow type before and after the atlas correction.

Results:
The mean age of the eleven migraine subjects (eight females) was 40.6 ($\pm$12.6) years. Total arterial in flows were the same at baseline and after the intervention. Four subjects exhibited increased secondary paraspinal venous flow (Type II) with decreased venous outflow via the internal jugular veins (Type I). By week-8, this cohort demonstrated an increase in hydrodynamic intracranial compliance index (7.9 to 9.8) following the atlas correction. At week-4, only the seven subjects exhibiting Type I flow showed a decrease in venous flow (t-test, $p=0.029$). Following the intervention, all subjects reported a measureable decrease in migraine symptomatology following the intervention.

Conclusion:
Apparent physiologic flow changes observed after the NUCCA intervention of two cohorts characterized by their venous outflow type, indicates need for further investigation. A larger subject

(Woodfield, cont'd)

pool with healthy controls is required for data comparisons in determining potential quantifiable responses to this chiropractic intervention.

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Keywords:
migraine headache, phase-contrast MRI, venous outflow, cerebrospinal fluid, NUCCA chiropractic

None of the authors have anything to disclose or any conflicts of interests in regards to this study.

Long-term follow up of multiple sclerosis patients who underwent venous angioplasty: A 5 year observational case series study

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Background: Chronic cerebrospinal venous insufficiency (CCSVI) has been proposed to be associated with multiple sclerosis (MS).

Objective: To describe the long-term extracranial venous hemodynamic and clinical outcome changes following venous angioplasty in MS patients.

Methods: The group consisted of 4 progressive (PMS) and 3 relapsing-remitting (RR) MS patients. The median time from baseline Doppler examination to the venous angioplasty procedure was 3 months. Six patients had their procedure performed in New York State and one in Poland. The follow-up Doppler examination was performed 5.6 years after the baseline exam using the same equipment and operator. The CCSVI diagnosis [≥2 venous hemodynamic (VH) criteria] was assessed at baseline and at follow-up. Because of technical changes in the CCSVI Doppler protocol between baseline and follow-up, we were able to compare only 3 venous hemodynamic (VH) parameters (presence of B-mode abnormalities or stenosis, no flow detection and negative Δ cross-sectional area) longitudinally. Therefore, modified venous hemodynamics severity score (mVHISS) criteria was used to assess the severity of the VH changes between baseline and follow up. Disability status was evaluated using Expanded Disability Status Scale (EDSS). Due to the limited sample size, analyses were restricted to descriptive comparisons.

Results: At baseline, 6/7 (86%) patients had a diagnosis of CCSVI and at follow-up 4/7 (57%) patients. The mVHISS had absolute change of 0.4 over the follow-up. EDSS increased from 4.0 to 4.5 in total MS group. In RRMS patients it remained relatively stable (2.0 at baseline and 2.2 at follow-up), while in PMS patients it increased (5.5 at baseline and 6.3 at follow-up).

Conclusion: Lees MS patients had diagnosis of CCSVI at follow-up. However, despite the intervention, their mVHISS score somewhat increased and their disability status continued to slightly worsen.

Keywords: multiple sclerosis, Doppler ultrasound, venous angioplasty, disability

Study disclosure:
This study was funded with internal resources of the Buffalo Neuroimaging Analysis Center. In addition, we received support from the Jacquemin Family Foundation.

Financial Relationships/Potential Conflicts of Interest:

(Jakimovski, cont'd)

Dejan Jakimovski, Karen Marr, Sirin Gandhi, Deepa P. Ramasamay, Ahmed Sanai, Rahil Ahmed, Jesper Hagemeier have nothing to disclose.

Bianca Weinstock- Guttman received honoraria as a speaker and as a consultant for Biogen Idec, Teva Pharmaceuticals, EMD Serono, Genzyme&Sanofi, Novartis and Acorda. Dr Weinstock-Guttman received research funds from Biogen Idec, Teva Pharmaceuticals,, EMD Serono, Genzyme&Sanofi, Novartis, Acorda.

Robert Zivadinov received personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health and Novartis for speaking and consultant fees. He received financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin-Coherus and IMS Health.

Bridging the Gap between Chronic Cerebro Spinal Venous Insufficiency (CCSVI) and Ménière Disease (MD)

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It is nowadays sufficiently demonstrated that Chronic Cerebro Spinal Venous Insufficiency (CCSVI) is very frequent in Ménière disease (MD). MD is a chronic illness of the inner ear that affects a substantial number of patients every year worldwide. Although Endolymphatic Hydrops (EH) is the worldwide accepted mechanism of MD, the causes that induce it are still not clear and MD has been correlated to a wide and different disturbances ranging from trauma to sleep disorders. Even if CCSVI may potentially induce EH through a pure "hydraulic" mechanism CCSVI per se does not explain how the various disorders correlated with MD may interact with CCSVI and provoke EH. The aim of this paper is an attempt to approach MD into the context of the more recent findings about the global brain waste clearance system, to which inner ear is anatomically and functionally connected, in order to build a reasonable model of MD pathogenesis. A review of literature regarding MD pathogenesis has been performed. On the basis of this review and personal experience we can state that the major part of the diseases correlated to MD may act on the inner ear disturbing the Glymphatic (GS) and/or Brain Lymphatic System (BLS) activity. Because the venous system interplays with GS and BLS, in the proposed model CCSVI is considered more than a direct cause of MD rather the anatomical predisposition to develop the disease. In this model EH, and then MD, is the consequence of a failure of the compensation of the congenital venous abnormalities, anatomical compensation as collateral pathways and/or functional compensation as GS and BLS. This model allows an unitary interpretation of MD pathogenesis and the major part of the disturbances correlated with MD may be appropriately approached.

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Key words: Ménière Disease; Chronic cerebrospinal venous insufficiency; Glymphatic System; Brain Lymphatic System; Hearing loss; jugular veins; vertigo

Conflict of interest: the authors declare no potential conflict of interest.

Bacterial and Protozoal Metagenomic Analysis of Peripheral Blood in 32 Multiple Sclerosis (MS) Patients by Next-Generation Sequencing

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Hypothesis:
The literature supports an inflammatory and parasitic correlation in MS. Our hypothesis is that non-human Eukaryotic organisms cause venous vascular obstruction thus resulting in reduced or altered CNS perfusion and flow resulting in the observation of CCSVI and resultant demyelination. One step in the proof of this hypothesis is to determine if these obstructive organisms are present in peripheral blood.

Background:
Clinical and epidemiological studies suggest that infectious agents may be involved in the pathogenesis of MS; research has additionally implicated a malaria-like organism [22-24]. A recent series of publications have implicated an obstructive process in the Cerebral Central Veins (CCV) of MS patients also called Chronic Cerebrospinal Venous Insufficiency (CCSVI).

Materials and Methods:
MS patients were recruited meeting the McDonald criteria. Normal controls were recruited in the community at large according to WIRB protocol # 1133561**.** Peripheral blood was obtained from MS and Normal Control patients. Fluorescence microscopy was used to document putative biofilm communities using Höechst DNA stain. DNA was extracted from 5mL of whole blood for Next-Generation Sequencing was performed utilizing the RIDI™ system (Fry Laboratories, L.L.C.) .

Results:
Microscopic and DNA analyses of peripheral blood from 32 MS and normal controls, we discovered and documented structures consistent with intravascular biofilm fragments that also contain DNA sequences for a variety of known and novel protozoa. Results from the metagenomic analysis suggest there could be differences in both the identity and the relative amounts of organisms present in the MS populations when compared to the normal control population. Several species of protozoa were identified that were not present in the control population and many of these organisms were significantly divergent (greater than 5%) than the closest published and named organism by homology.

Summary:
Existing and potentially novel Eukaryotic organisms were identified in patients with MS and there is a population difference compared to normal controls. Bacteria were identified but they were usually in low numbers. We feel that this study was successful in proving a first component of our vascular hypothesis that potential non-human eukaryotes are present.

Dr. Fry has nothing to disclose nor any conflicts of interests to declare in regards to this study.

De Novo approach in treatment of chronic migraine and trigeminal neuralgia

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Synopsis:
The patient centered outcomes of this prospective pilot study is to evaluate the efficacy and safety of administration of dexamethasone, lidocaine, and thiamine into the branches of trigeminal nerve , the greater and lesser Occipital Nerve simultaneously for treatment of trigeminal neuralgia and migraine. We hypothesized that peripheral nerve system is nourished by vasa nervorum of arterial and venous system. Vasa nervorum per se controlled by sympathetic and parasympathetic network complex embedding into adventia and muscularis layer of vessel, which genetically equilibrates its function toward physical world by silencing and desilencing of bio signals, which play major role in production of pain?

Purpose:
To measure the simultaneous effect of dexamethasone/lidocaine/thiamine administration into the trigeminal nerve branches as well as greater/lesser occipital nerve, in patients with intractable chronic migraine headaches, with and without of aura, ophthalmoplegia, and lingual apoplexy, in long term pain relief.

Method:
Patients were randomly selected by approach in acute migraine attack at our clinic. Informed consent obtained. A sterile mixture of medication prepared and administered simultaneously to the all exposed branches of trigeminal nerve and greater and lesser occipital nerves. Patients followed up per protocol.

Results:
Patients responded with complete relief after being treated with dexamethasone/ lidocaine/thiamine mix in one session. Of the 40patients treated, 95% reported major relief without any adverse reaction, with two of the 40 patients reporting relapse. Longest migraine free period reported by patients: 65 months. Average number of migraine free time: 15.24 months. Percentage of patients with complete pain relief: 95%, however 5% reported major relief of migraine symptoms with episodic relapsing pain. No adverse reactions reported.

Conclusion:
De-Novo one session treatment is safe and provides long-term pain relief. Tolerable for children too and adult.

Dr. Owiesy has nothing to disclose nor any conflicts of interests to declare in regards to this study.

Assessing the biofilm characteristics and to map the metagenome in arterial plaque.

Dr. Stephen E. Fry
Fry Laboratories

BACKGROUND: Evidence that vascular inflammation is an important mechanism involved in all stages of atherogenesis continues to accumulate. We hypothesize that common complex microbial involvement may be present in atheromatous debris removed from treated lesions. We evaluated this debris with metagenomic analysis.

OBJECTIVES: To assess the biofilm characteristics and to map the metagenome in arterial plaque.

METHODS: After informed consent, fifteen cases of vascular aspirate or explanted embolic filters were examined. Thirteen cases were in patients undergoing carotid stenting (3 MoMa, 10 embolic filters). One case was in a saphenous vein graft intervention (aspirate and filter) and one case was after SFA orbital atherectomy (aspirate and filter). Fluorescence microscopy, bacterial and protozoan metagenomic analysis using the RIDI™ Next Generation Sequencing (NGS) analysis system, and specific protozoan multiplex PCR probes were used to assess the presence and composition of biofilm populations.

RESULTS: Bacteria were not detected in peripheral blood; however, 4 of 12 filters and 2 of 5 atheroma debris samples had identified bacterial populations (2 patients had atheroma debris and filter evaluated). Evidence of protozoan populations was obtained in 4 of 15 peripheral blood samples, 11 of 12 filters and 4 of 5 atheroma debris samples. Microscopy illustrated a complex composition of biofilm communities in blood, devices, and atheroma debris samples. The identified bacterial taxa in atheroma debris suggested a diverse and novel population composition. Biofilm dwelling bacteria, while present in several atheroma or filter samples, were not detectable in peripheral blood and were not universally present in atheroma or filter. Taxonomic comparisons of sequenced protozoa are consistent with a diverse array of organisms similar to poorly characterized environmental protozoa.

CONCLUSION: Of 15 patients, 6 patients had evidence of bacteria and 13 had evidence of protozoa in debris and 14 exhibited evidence of complex biofilm communities. This data suggests biofilm forming protozoa may play a key role in arterial vascular disease.

Keywords: plaque, biofilm, arterial, sequencing, protozoa

Dr. Fry has nothing to disclose nor any conflicts of interests to declare in regards to this study.

7 Annette Funicello Research Fund for Neurological Diseases – ABSTRACTS

A case-control, 5-year follow-up study of cardiovascular, environmental and genetic risk factors for disease progression in patients with MS (CEG-MS study)

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Background: Progression of multiple sclerosis (MS) is related to underlying cardiovascular (CV) comorbidities. MS patients with more than one CV risk factor at the time of diagnosis had an increased chance of ambulatory disability and brain tissue injury, and the risk increases with the number of CV risk factors. No previous longitudinal studies investigated how extracranial arterial and venous disease is related to progression of MS over time.

Objectives: To identify the role of presence and severity of extracranial arterial and venous disease with respect to clinical progression in clinically isolated syndrome (CIS) and MS patients, as compared to healthy individuals (HI) and patients with other neurological disease (OND) over 5 years.

Methods: This is a prospective and ongoing study of subjects that participated in the original cardiovascular, environment and genetic (CEG) MS study. All subjects were assessed at baseline and will be assessed at the 5-year follow-up using the same 3T MRI and arterial and venous hemodynamic (VH) extra-cranial and trans-cranial Doppler examinations. Additional assessments will include neuropsychological, clinical, environmental, laboratory blood, and optical coherence tomography (OCT) examinations. The inclusion criteria for the 5-year follow-up study are: a) having an MRI 3T standardized scan at baseline, b) age 18-85 years, c) being resident at baseline examination in the New York State, and c) signed informed consent. Exclusion criteria are: a) nursing mothers or pregnant women, b) unwillingness or inability to comply with the requirements of this protocol, and c) any other reasons that, in the opinion of the Investigator, indicate that the subject is unsuitable for enrollment into this study.

Results: Of the 1,111 subjects with CIS, MS, HCs and OND enrolled at baseline, 583 subjects were eligible for the 5-year follow-up study according to the inclusion criteria. Among those, 110 HI, 250 MS patients, 35 CIS patients and 35 OND patients are expected to be recruited at the 5-year follow-up. As of April 1, 2016, 207 subjects signed the informed consent, and were included in the CEG-MS follow-up study, while 30 declined participation and 51 were unreachable. Seven self-withdrew their informed consent. The follow-up will continue until mid-2018. The preliminary data on first 87 MS patients and 36 HCs will be presented.

Conclusions: CEG-MS 5-year follow-up study represents first longitudinal and prospective study of monitoring influence of arterial and venous disease risk factors for progression in MS.

Key words: multiple sclerosis, longitudinal, prospective, Doppler ultrasound, MRI

(Zivadinov, cont'd)

Study disclosure:

This study was funded with internal resources of the Buffalo Neuroimaging Analysis Center. In addition, we received support from the Annette Funicello Research Fund for Neurological Diseases, Jacquemin Family Foundation and smaller donations.

Financial Relationships/Potential Conflicts of Interest:

Robert Zivadinov received personal compensation from Teva Pharmaceuticals, Biogen Idec, EMD Serono, Genzyme-Sanofi, Claret Medical, IMS Health and Novartis for speaking and consultant fees. He received financial support for research activities from Teva Pharmaceuticals, Genzyme-Sanofi, Novartis, Claret Medical, Intekrin-Coherus and IMS Health.

Combined study of neurodegeneration, cerebrovascular reactivity and venousdrainage impairments in Parkinson's Disease and Multiple Sclerosis

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Background
Recent studies suggested that altered cerebrovascular reactivity (CVR) and perfusion may be linked to neurodegeneration in multiple sclerosis (MS)[1] and Parkinson's Disease (PD)[2]. Moreover, in these patient populations, alterations in the extra-cranial venous vasculature have also been observed [3,4]. These two aspects have generally been studied independently. However, impairment of venous outflow from the brain may potentially lead to intra-cranial vasculature changes in the form of altered perfusion and CVR.

Objectives
To investigate in a cohort of MS and PD patients if drainage impairment and perfusion/CVR are associated.

Methods
For this two year project, we planned to recruit 25 MS, 20 PD patients and 40 age and sex matched healthy controls (HC).

Each subject underwent: 1) neurological examination; 2) B-mode and PW Doppler ultrasound exam for Internal Jugular Vein (IJV) morphological assessment; 3) MRI protocol (1.5T Siemens scanner) including T1-3D for tissue volumetry, FLAIR, dual echo spin echo for lesion load quantification, arterial spin labeling (ASL) at normocapnia and hypercapnia (5%CO_2) for brain perfusion evaluation, time of flight for IJV identification and phase contrast for the main neck vessels flow quantification. End-tidal CO_2 ($etCO_2$) values and respiration rates were measured during ASL acquisition.
ASL images were processed with FSL (http://fsl.fmrib.ox.ac.uk/fsl/) for the computation of cerebral blood flow (CBF) maps during normocapnia and hypercapnia. The CBF maps were registered to the corresponding T1-3D and to a common (MNI) space. Phase contrast images were processed with SPIN software (http://www.mrinnovations.com/).The examination required the work of a multidisciplinary team (radiologists, neurologists, engineers, MRI technician).
The preliminary statistical analyses were the following. The IJV area and flow differences between the MS and HC groups were tested using Mann Whitney non-parametric test. A voxel-wise statistical analysis of the MNI-aligned CBF maps was performed in order to test: 1) differences between MS and HC at normocapnia; 2) correlation with IJV flow at normocapnia; 3) differences between normocapnia and hypercapnia; 4) CVR differences between MS and HC. The alpha level of 0.05 was considered significant.

(Lagana, Cont'd)

Results
From July to September 2015, the setting for the MR examination at hypercapnia was prepared and preliminarily tuned in five healthy subjects. From September 2015 to March 2016, 20 MS patients (10 males, 41±12 years), 20 age matched HC (11 males, 42±15 years), 4 PD (3 males, median age=66, range=55-75 years), and 5 elderly HC (1 males, median age=73, range=70-75 years) were examined. The MS median [range] EDSS was 1.5 [0-6.5]; disease duration 8.5 [2-36] years; lesion load 4.3±6.2 ml. One MS and three HC did not complete the MR ASL at hypercapnia.
Ultrasound measures showed significantly smaller ($p<0.001$) IJV area in MS (median [25th-75th percentile]=0.2 [0.1-0.5] cm^2) compared to HC (0.5 [0.3-0.8] cm^2). Two MS and two PD patients had unilateral IJV atresia, revealed by ultrasound and TOF images.

The preliminary analysis of ASL images in normocapnia showed a reduced perfusion in the left anterior cingulate and paragingulate gyri and in the left thalamus for MS compared to HC. A global positive correlation was found between brain CBF and IJV flow rate in HC, whereas in MS the correlation was only in the left hemisphere, in particular in insular cortex, operculum, and inferior frontal gyrus, middle and superior temporal gyri.

A significant global increase of brain perfusion was observed at hypercapnia compared to normocapnia in MS and HC. The CVR was not statistically different between MS and HC.

Conclusion
Our preliminary analyses showed that in HC there is a widespread relationship between brain perfusion and venous flow rate, which seems to be lost in MS with the exception of a few temporal areas. The protocol for assessing neck flow and cerebral blood flow in normocapnia and hypercapnia showed to be feasible also for PD patients. Therefore, this approach is promising for the non-invasive study of the relationship between extra-cranial drainage changes and the pattern of brain perfusion in different neurodegenerative diseases.

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Keywords
Neck flow, cerebral blood flow, cerebrovascular reactivity, arterial spin labeling.

Conflict of interest: the authors declare no potential conflict of interest.

Brain Endothelial derived microparticles as mediators of neurovascular/neurodegenerative diseases

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Background: Despite the high metabolic rate and neuronal sensitivity to waste products, the brain lacks a conventional lymphatic system that mediates the removal of toxic waste and other mediators. We have however demonstrated lymphatic-specific proteins in human brain tissue as well as in serum samples, with altered expression levels in multiple sclerosis (MS).

Objective: We investigated the effects of pro-inflammatory cytokines on the expression of neurolymphatic biomarkers in brain endothelial cells (BECs) and in microparticles (MPs) released by BEC, as well as effects of MPs on brain smooth muscle cell (SMC) contractility.

Methods: Human (hCMEC-D3) and murine (bEnd.3) BECs were treated with TNF-α (20 ng/ml) and/or Interferon-γ (1000 U/ml) for 48 hours and numbers of MPs shed from cells under different conditions analyzed using flow cytometry. Neurolymphatic biomarker expression was determined using western blotting and spatial distribution patterns analyzed using immunocytochemistry. SMC contraction was analyzed in human brain vascular smooth muscle cells (HBVSMC) with culture medium supplemented with BEC basolateral microparticles (BMPs).

Results: BECs released MPs from both apical and basolateral domains. BECs expressed neurolymphatic biomarkers that were transferred into MPs following TNF-α/IFN-γ stimulation. Interestingly, T/I stimulation also potently induced the transfer of caveolin-1, an important caveolar constituent, from BECs into MPs. BMPs produced by hCMEC-D3 under normal conditions inhibited HBVSMC contraction and BMPs derived from cells under inflammatory condition further inhibited contraction.

Conclusion: These findings suggest that pro-inflammatory cytokines indeed influence neurolymphatic protein expression in BECs and MPs. The altered neurolymphatic marker expression observed in forms of MS may represent partitioning of these biomarkers within caveloae-rich MPs that segregate signaling modules related to neurovascular disease.

Support: ***AFRF for Neurologic Research***

A randomised, double-blinded, controlled study with sham and crossover, of Percutaneous Transluminal Angioplasty (PTA) for extracranial vein stenoses in patients with Multiple Sclerosis.

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Objectives: To report on the study design and interim findings of the safety and efficacy of venous PTA in MS patients with extracranial venous abnormalities.

Methods: The study was randomised, double-blinded, controlled with a sham procedure and incorporated Magnetic Resonance Imaging (MRI), multimodal venous imaging - duplex Ultrasound (dUS), Magnetic Resonance Venography (MRV) and Digital Subtraction Angiography (DSA), and measurement of disability, cognition, fatigue and Quality of Life.
Patients were randomized into the treatment or control arm and followed up for 24 months. Patients in the control arm crossed over to the treatment arm at 12 months. The patients, the consulting neurologists and radiologists reading the images were blinded to the time of the PTA procedure. Primary endpoints were safety at 24 hours, 1, 6, 12, 18 and 24 months and restoration of venous flow, post procedure and at 6, 12, 18 and 24 months. Secondary endpoints included clinical parameters and disease progression as measured by Kurtzke Extended Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite Score (MSFC), the Cognitive Assessment Tool (CogState) at 1, 3, 6, 12, 18 and 24 months, MRI at 6 12, 18 and 24 months, patient reported Quality of Life (MSQoL-54) and fatigue measured by the Fatigue Severity Scale (FSS) at baseline, 1 week, 1, 3, 6 12, 18 and 24 months. Fentanyl sedation was used for the procedures with Midazolam for blinding. Staff were instructed to minimise discussion during procedure and total time in the angiography suit was at least 1 hour for all cases.

Results: 36 patients were consented and 28 were enrolled. No extracranial venous abnormalities were observed in 4/32 (12.5%) with DSA, however one of these patients was found to have abnormalities with dUS. 5 were lost to follow-up, 3 at 6 months and 1 at 12 and one at 18 months. There were two cases of relapse during the study, one occurred 3 months post the sham procedure, this patient had relapsed 7 months prior to entering the study. The second patient had more frequent tingling sensation to the back of the head after the initial PTA. There were no other serious adverse events related to the study, study related adverse event included haematoma (2), groin pain (1), neck pain (4), and cannulation pain (1). There was a large variation in response to treatment and the sample size is too small to be able to detect any significant difference between the groups. A trend to a difference between the groups was found with the EDSS and 2/7 components of the CogState tests. There was an improvement in the reported Quality of Life in the treatment arm compared to controls. Analysis of the difference in the imaging modalities has not been completed.

Conclusion: No conclusions can be drawn from this interim analysis.

Support: ***AFRF for Neurologic Research***

8 ACKNOWLEDGEMENTS of SUPPORTERS & CORPORATE MEMBERS

We gratefully acknowledge the following companies and organizations for providing grant support for quality medical education.

This live activity is supported by grants from:

Canadian Coalition for the Study of Venous Insufficienc

Barrie Vascular Imaging

MR INNOVATIONS

CCSVI Alliance
opening veins, opening minds

Jeff Beal Music, Inc.

THE Annette Funicello RESEARCH FUND FOR NEUROLOGICAL DISEASES at the California Community Foundation

The Family of Mr. Lafayette Rogan Jones, Jr.

In Loving Memory of Mr. Lafayette Rogan Jones, Jr.